AMERICAN HEART JOURNAL

AN INTERNATIONAL PUBLICATION
FOR THE STUDY OF THE CIRCULATION

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VOLUME 50
JULY-DECEMBER, 1955

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THE C. V. MOSBY COMPANY
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Printed in the
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Press of
The C. V. Mosby Company
St. Louis

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VOL. 50 JULY, 1955 No. 1

UNIVERSITY OF MICHIGAN

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Vol. 50, No. 1, July, 1955, American Heart Journal is published monthly, by The C. V. Mosby Company, 3207 Washington Avenue, St. Louis 3, Missouri, entered as second class matter January 23, 1917 at the Post Office at St. Louis, Missouri, under the Act of March 3, 1879. Additional entry authorized at Jefferson City, Missouri. Subscription Price: United States, and its Possessions, per year $12.00; Canada $13.00; Foreign $13.50. Printed in the U. S. A. Copyright 1955 by The C. V. Mosby Company.

American Heart Journal

VOL. 50 JULY, 1955 No. 1

Original Communications

THE CLINICAL SYNDROMES IN PATENT DUCTUS ARTERIOSUS

IVAN J. PINTO, M.D.*

CHICAGO, ILL.

PATENT ductus arteriosus (P. D. A.), the simplest congenital anomaly of the heart, from several viewpoints, may nevertheless present itself to the physician in one of a number of distinct clinical patterns. Acoustically cases of P. D. A. may have a continuous murmur, a systolic murmur and diastolic murmur, only a systolic murmur, or no murmur at all in the pulmonary area. The occurrence of an apical diastolic murmur has been noted in some cases[5,7,11,20] in the absence of organic damage to the mitral valve. Electrocardiographically cases of P. D. A. have been reported with a normal electrocardiogram, with right-heart strain, combined heart strain, left-heart strain, or with right bundle branch system block. Radiographically the heart may be normal, or there may be right or left ventricular enlargement; the pulmonary arteries may be normal in size or dilated, and the peripheral vascular lung fields may or may not be hypervascular.

Hemodynamically the pulmonary arterial pressures may be normal or elevated. There may be a large shunt or a small one; the shunt may be from right to left, from left to right, or in both directions.

The opportunity to review carefully all cases of P. D. A. studied by this department has led to a classification of the various ductus syndromes on the basis of auscultatory findings. This was compared to and correlated with the material in the literature and forms the substance of this report. Such a classification is useful primarily because of its applicability to bedside differential diagnosis. The physical findings of such cases are interpreted in terms of data

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Aided in part by the Hibse Heart Fund and the Michael Reese Research Foundation.

Received for publication Oct. 29, 1954.

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TABLE I

GROUP	CLINICAL FEATURES	AUSCULTATORY FINDINGS	ELECTROCARDIOGRAM, FLUOROSCOPY, AND X-RAYS	PHYSIOLOGIC FEATURES	DIFFERENTIAL DIAGNOSIS
A 1	Usually asymptomatic	*Pulmonary area:* continuous pulmonary murmur; second sound normal *Apex:* diastolic murmur absent	Normal electrocardiogram; normal heart size; hilar dance	Small left-to-right shunt; normal pulmonary arterial pressures	Aortic insufficiency; pulmonary insufficiency; aortopulmonary septal defect; ruptured aneurysm of the right anterior aortic sinus of valsalva; ventricular septal defect; truncus arteriosus
A 2	Symptoms early in infancy; repeated bouts of upper respiratory tract infection or congestive heart failure; wide pulse pressures	*Pulmonary area:* continuous murmur; pulmonary second sound soft *Apex:* diastolic murmur present	Left heart strain; left ventricular enlargement; pulmonary artery enlarged; hilar dance; increased vascularity of lung fields	Large left-to-right shunt; normal pulmonary arterial pressures	Coarctation of the aorta; pulmonic stenosis; glycogen storage disease; aberrant coronary artery idiopathic myocarditis, fibroelastosis
B 1a	Limitation of cardiac reserve; palpable second pulmonary heart sound (diastolic shock); right ventricular heave	*Pulmonary area:* systolic, systolic and diastolic murmur; accentuated pulmonary second sound *Apex:* apical diastolic murmur absent	Right heart strain; enlarged right ventricle; pulmonary artery enlarged; increased vascularity of lung fields; hilar dance	Small left-to-right shunt; elevated pulmonary arterial pressures	Aortopulmonary septal defect, with pulmonary hypertension; atrial and ventricular septal defect; pulmonic stenosis; coarctation of the aorta with pulmonary hyertension
B 1b	Symptoms generally in third or fourth decade; limitation of cardiac reserve with right heart failure; deeper cyanosis in the feet than right hand and face; cyanosis of the feet increases with exercise	*Pulmonary area:* systolic, systolic and diastolic murmur; accentuated pulmonary second sound *Apex:* diastolic murmur absent	Right heart strain; enlarged right ventricle; enlarged pulmonary arteries; peripheral constriction of vessels in the lung field; calcification in some arteries; hilar dance	Variable right-to-left shunt increased with exercise and anoxia; blood from femoral arteries more desaturated than right brachial artery; pulmonary arterial pressures higher than aortic	Eisenmenger's syndrome; aortopulmonary septal defect with reversed shunt; atrial septal defect with chronic cyanosis; truncus arteriosus
B 2	Same as Group B, 1a but occurs in a younger age group	*Pulmonary area:* atypical murmur; pulmonary second sound accentuated or split *Apex:* diastolic murmur present	Combined heart strain; increased transverse diameter of the heart; pulmonary arteries enlarged; increased vascularity of the lungs and hilar dance	Large left-to-right shunts; elevated pulmonary arterial pressures	Mitral stenosis, in addition to those from which Group B 1a have to be differentiated
C	Usually in congestive heart failure; any age group	No murmurs Heart sounds vary	Varies	Varies	Varies

obtained by cardiac catheterization. The mechanisms involved in the production of the murmurs of P. D. A. are reported separately.[18]

Whenever possible, the various subgroups of the classification have been illustrated with appropriate case histories.

CLASSIFICATION OF PATENT DUCTUS ARTERIOSUS BASED UPON AUSCULTATORY FINDINGS (TABLE I)

A. *Cases* with typical continuous murmurs at pulmonic area
   1. Without diastolic murmurs at the apex
   2. With diastolic murmurs at the apex

B. *Cases* with atypical murmurs at the pulmonic area
   1. Without diastolic murmurs at the apex
      (a) No cyanosis
      (b) Cyanosis due to reversal of shunt
   2. With diastolic murmurs at the apex

C. *Cases* without murmurs at the pulmonic area

Group A: *Type 1.*—Typical continuous murmur at the pulmonary area. No apical diastolic murmur. Example: Case 1.*

Examples of this group occur at any age. Most of these cases are asymptomatic, and are diagnosed accidentally by detection of the classical murmur on routine medical examination. This group is the most common and generally represents about 90 per cent of all cases of P. D. A.

At the pulmonary area, the typical continuous murmur is present, and its onset is separated from the first sound by a definite interval. The murmur increases in intensity up to the second pulmonary sound with a late systolic accentuation[12,15] and then decreases again until it can be hardly audible toward the end of diastole. This murmur has a characteristic machinery quality, and is generally accompanied by a thrill. The second pulmonary sound is lost in the murmur. The continuous murmur is the most important sign in the diagnosis of P. D. A.[8,9,19] At the apex a systolic murmur occurs, which is also separated from the first heart sound by a distinct interval. The radiographs and electrocardiograms are normal. The left-to-right shunt is small, and the pulmonary arterial pressures are normal.

Such cases have to be differentiated from other anomalies that give rise to a continuous murmur or to a to-and-fro murmur at the pulmonary area. These include aortic stenosis with incompetence, the functional Graham Steell murmur, aortopulmonary septal defect, ventricular septal defect, ruptured aneurysm of the right anterior aortic sinus of Valsalva, and truncus arteriosus.

In aortic stenosis and incompetence the murmur begins immediately after the first heart sound, and is high pitched. It increases in intensity during systole and diminishes again prior to the onset of the second sound. It waxes and wanes again in diastole. This waxing and waning, both in systole and diastole,

*All case histories are assembled in the Appendix.

imparts a peculiar "sea gull" quality to this murmur. There is also an associated diminished intensity of the second aortic sound.

The continuous murmur of aortopulmonary septal defect resembles that heard in P. D. A. However, it may be of a greater intensity, and the site of maximum intensity may be at a slightly lower level.[10] In cases of aortopulmonary septal defect with a continuous murmur the pulmonary arterial pressures appear to be normal often.

Fluoroscopically the ascending portion of the aortic arch pulsates more vigorously than the arch.[4] The diagnosis can be suggested by retrograde aortography.

Rarely, an interventricular septal defect may have a continuous murmur at the pulmonary area, indistinguishable from that heard in cases of P. D. A. Morgan and Burchell have reported such a case.[17] The diagnosis can usually be established by cardiac catheterization. Careful examination of the simultaneously recorded carotid artery pulse pressures and phonocardiograms reveals that the systolic accentuation of the murmur precedes the upstroke of the carotid pulse wave, while in P. D. A. the systolic accentuation is synchronous with the upstroke of the carotid pulse wave.

In ruptured aneurysm of the right anterior aortic sinus of Valsalva a continuous murmur may be heard at the pulmonary area. This murmur has a rough sawing quality, and the thrill is marked. These murmurs appear relatively close to the chest wall and the point of maximum intensity is definitely at the base of the heart over the middle of the precordium.[1]

In truncus arteriosus a continuous murmur is often present which is identical with that heard in P. D. A. Cyanosis is always present in these cases. The second pulmonary sound is "pure." The supracardiac shadow may be prominent in the posteroanterior view. There is a prominent shelf in the left anterior oblique. Cardiac catheterization demonstrates peripheral arterial unsaturation. Angiocardiography reveals a single vessel from which the pulmonary arteries and systemic arteries arise.

Group A: Type 2.—Continuous murmur at the pulmonic area with an apical diastolic murmur. Example: Cases 2 and 3.

These patients usually present themselves as diagnostic problems in early infancy. They are somewhat underdeveloped and suffer from repeated attacks of upper respiratory tract infection and congestive heart failure.[16,26] The striking physical finding in these patients is a continuous murmur at the pulmonic area. P_2 is rarely audible as a sound distinct from the murmur, with the result that the condition is sometimes misdiagnosed as pulmonic stenosis. There is an apical diastolic murmur which ends in a normal first heart sound. These patients have wide pulse pressures. Radiographic examination shows an enlargement of the pulmonary arteries with a hilar dance. The peripheral lung fields are hypervascular. There is an enlargement of the left ventricle. In some cases enlargement of the left atrium can be demonstrated by the deviation of the barium-filled esophagus. The electrocardiogram shows left-heart strain. There is a large left-to-right shunt, with normal pulmonary arterial pressures. The prognosis of these cases is grave. They end fatally if the P. D. A. is not corrected surgically.

These patients must be differentiated from instances of acyanotic heart disease that cause congestive heart failure like coarctation of the aorta, from pulmonic stenosis, when the P_2 is of such a low intensity that it is lost in the murmur, and a group of myocardial diseases including glycogen storage disease, aberrant left coronary artery disease, necrosis of the pulmonary artery, idiopathic myocarditis, and fibroelastosis. These latter conditions are characterized by congestive cardiac failure and left-heart strain.[21]

Coarctation of the aorta resembles P. D. A. in that electrocardiographically there is left-heart strain, and congestive heart failure occurs in some cases. However, a systolic murmur, which begins a short interval after the first heart sound, is present at the pulmonary area. The second pulmonary heart sound can be heard distinctly. The pulses in the femoral vessels may not be felt. The blood pressure is lower in the legs than in the arms.

In pulmonic stenosis the systolic murmur begins immediately after the first heart sound, and ends before P_2. The latter is diminished in intensity or often absent. The right ventricular heave is palpable, and the electrocardiogram shows right-heart strain.

The other conditions mentioned are rare. There are no murmurs present. In glycogen storage disease the onset of congestive heart failure is usually in the first three months of life. Muscle biopsy may show an increase in muscle glycogen. There is a positive family history. The electrocardiogram in aberrant coronary artery disease resembles more the one seen in myocardial infarction than left-heart strain. These patients also give a history of distress while nursing. Idiopathic myocarditis has a relatively later onset of congestive heart failure which responds well to large doses of digitalis. Gallop rhythm is usually present.

Group B: *General Factors.*—The acoustic findings in this group are varied. The murmur is described as "atypical" because it does not have the characteristics of the continuous "machinery murmur" which is associated in the minds of clinicians with the presence of a P. D. A. At the pulmonary area, the diastolic element of the continuous murmur may be truncated, only a systolic murmur may be present, or there may be a to-and-fro murmur. All cases are associated with an accentuated or reduplicated second pulmonary heart sound as a result of pulmonary hypertension.[24] This may be due dynamically to a heightened pulmonary arterial diastolic pressure operating to reduce the volume of flow, and thereby the velocity across the shunt.

In some cases the pulmonary arterial pressures may be increased sufficiently to cause an actual reversal of shunt,[6] resulting in an uneven distribution of cyanosis. The clinical characteristics of this latter group with reversed shunt are different from the other types in this group and will be discussed separately.

Group B: *Type Ia.*—Atypical murmur at the pulmonic area. No apical diastolic murmur. No cyanosis. Example: Case 4.

The clinical characteristics of this group may be summarized as follows: They occur at any age and are associated with a limitation of cardiac reserve.[13] The murmur may be, as discussed previously, systolic, or a systolic and diastolic, but is always associated with an accentuated or split P_2. A systolic murmur

may be heard at the apex. On palpation a diastolic shock may be felt, in the second left intercostal space, and the right ventricular heave may be palpated in the third and fourth intercostal spaces over the left lateral parasternal line. The electrocardiogram shows right-heart strain. Radiographically the pulmonary arteries are enlarged, and a hilar dance is present. The vascularity in the peripheral lung fields is diminished. There may be evidence of left and right ventricular enlargement. Catheterization studies reveal that the pulmonary arterial pressures are raised. The left-to-right shunt is not considerable.

Differential diagnosis in this group includes aortopulmonary septal defect with pulmonary hypertension, interatrial and interventricular septal defect, pulmonic stenosis, coarctation of the aorta with pulmonary hypertension.

The aortopulmonary septal defect is differentiated by the characteristic features described previously. The same factors are concerned in the alteration of the continuous murmur in these cases as in P. D. A.

Both the interatrial and interventricular septal defect can be differentiated by the location and transmission of the murmur. In these two conditions the murmur is usually loudest at the third intercostal space at the left parasternal line. The systolic murmur is louder in the first intercostal space than in the fifth intercostal space in P. D. A. while the reverse is true in the other two conditions. In interatrial septal defect the P_2 is markedly split.[25] In interventricular septal defect the intensity of P_2 is normal or diminished unless pulmonary hypertension is present.

Coarctation of the aorta with pulmonary hypertension acoustically presents special problems in differential diagnosis. Here too, there is a delay in the onset of the systolic murmur which ends in an accentuated second sound in the pulmonary area when pulmonary hypertension is present. Besides the differentiating features described previously, patients with coarctation of the aorta develop signs of collateral circulation at this age. This can be recognized better by examining the patient with his head bent forward and with his arms hanging at his sides.[3] Radiologic findings include notching of ribs and occasionally a double prominence in the region of the aortic knuckle.[2]

The salient features in the differential diagnosis of pulmonary stenosis have been discussed.

Group B: *Type 1b.*—Atypical murmur at the pulmonary area. No apical diastolic murmur. Cyanosis. No case of this group was encountered in our series.

Patients in this group present the following features; these occur in the third and fourth decades. Progesssive limitation of cardiac reserve terminating in congestive heart failure is present. Cyanosis is more prominent in the legs than in the right arm and face. The cyanosis is increased with exertion and hypoxia. This uneven distribution of the cyanosis is due to the fact that P. D. A. is inserted below the origin of the innominate artery and above the origin of the left subclavian. These cases in addition show signs of pulmonary hypertension and right ventricular hypertrophy as listed previously. Radiographically they have enlarged hearts and dilated pulmonary arteries, with calcification in

the major branches of the pulmonary artery. Electrocardiograms show right-heart strain or right bundle branch system block. Determination of the oxygen content of the arterial blood reveals an O_2 content of the femoral artery which is less than that of the right brachial artery. The pulmonary arterial pressures are elevated and exceed the pressures in the aorta. The right-to-left shunt may be large or small depending on the pulmonary-aortic pressure difference, and the size of the ductus.[6]

The differential diagnosis of these cases includes cyanotic heart disease with pulmonary hypertension, like Eisenmenger's complex, interatrial septal defect with chronic cyanosis,[22] and aortopulmonary septal defect with reversed shunt.[4]

The most reliable way of differentiating these conditions is by cardiac catheterization. P. D. A. is the only condition in which the blood in the femoral artery is more desaturated than in the right brachial artery.

Group B: *Type 2.*—Atypical murmur at the pulmonary area with apical diastolic murmur. Example: Cases 5 and 6.

These cases generally occur in a younger age group. They are underdeveloped and are subject to repeated attacks of congestive heart failure. The auscultatory findings in the pulmonary area are similar to those of Group B, Type 1. However, the important difference is the presence of an apical diastolic murmur. In these cases the pulmonary arterial pressures are raised, and there is a larger left-to-right shunt than in the other types.

The differential diagnosis includes mitral stenosis in addition to anomalies giving rise to a systolic murmur at the pulmonary area discussed previously. Often the diagnosis between these conditions can only be settled by cardiac catheterization.

Group C.—No murmur.

In early infancy, the P. D. A. may be completely silent acoustically, and yet give rise to symptoms of congestive heart failure. This was true in Case 5. In such cases the murmurs may subsequently appear when the congestive heart failure responds to treatment.[14,16,23] Aneursymal dilatation of the ductus may also lead to a disappearance of the murmur.

GENERAL DISCUSSION

From the foregoing discussion it becomes quite clear that the varied acoustic findings are dependent on changes in pulmonary arterial pressure[13,18] and the volume of flow across the shunt. A careful evaluation of these acoustic findings will therefore give an idea of the size of the ductus and indicate the urgency of an operation.

In cases belonging to Group A, Type 1, there is a continuous murmur at the pulmonary area. This indicates that the shunt across the ductus occurs both in systole and diastole. The volume of flow across the shunt is not sufficient to cause an apical diastolic murmur. This indicates that the ductus is small. Operation in these cases is indicated due to the danger of the development of subacute bacterial endocarditis, but it is not an urgent procedure.

Cases in Group B, Type 1a, have an atypical murmur at the pulmonary area. This alteration of the continuous murmur is the result of an elevated pulmonary arterial pressure. These cases should be operated on as early as possible since pulmonary hypertension is progressive and terminates in right-heart failure. Surgical correction has in some cases led to a return of the pulmonary arterial pressures to normal.

Cases in Group A, Type 2 and Group B, Type 2, have in common an apical diastolic murmur. This indicates that there is a large volume of shunt across the ductus. In Group A, Type 2, the aortic-pulmonary pressure gradient exists both in systole and diastole while in Group B, Type 2, the aortic-pulmonary pressure gradient permits a flow only in systole. Thus, a large shunt occurs in systole only. This could only result from the presence of a ductus of a large diameter. This is well illustrated in Case 6 where the ductus found at operation was of a larger diameter than the pulmonary artery and the aorta. A diastolic murmur at the apex denotes a large left-to-right shunt through a large ductus. In infants belonging to this group, surgical correction is a lifesaving procedure. In all cases of P. D. A. with an apical diastolic murmur surgical correction is an urgent procedure.

SUMMARY

1. The clinical syndromes of P. D. A. have been described and illustrated with appropriate case histories. A clinical classification on the basis of auscultatory findings is presented.

2. The relationship between the auscultatory findings, the volume of the shunt, and the size of the ductus have been discussed.

3. Principles governing the urgency for surgery have been outlined.

SUMMARIO IN INTERLINGUA

Es describite le syndromes clinic de patente ducto arteriose. Le varie typos es exemplificate per pertinente casos illustrative. Un classification clinic de iste typos es elaborate super le base de datos auscultatori.

Es discutite le relation inter (1) le datos auscultatori e (2) le volumine del derivation e le dimensiones del ducto.

Un continue murmure ab le area pulmonar corresponde a un derivation occurrente tanto in le systole como etiam in le diastole. In casos ubi le fluxo non es grande, un murmure diastolic al apice pote mancar. Sub iste conditiones le intervention chirurgic non es urgente. Un reducite duration del murmure diastolic indica un elevation del pression pulmono-arterial e assi un progredente hypertension pulmonar. In tal casos un prompte intervention chirurgic es indicate pro obviar progressive cambiamentos pulmono-vascular.

I am indebted to Drs. L. N. Katz, E. Silber, S. Rodbard, and A. Shaffer for their advice in preparing this report, to the physicians whose cases are reported for permission to use them, and to the catheterization team for the data they obtained.

APPENDIX: CASE REPORTS

CASE 1.—(Group A, Type 1), J. M. This was a 4-year-old normally developed child in no distress. The child was asymptomatic, and a murmur was picked up in routine physical examination. This child was admitted to the Michael Reese Hospital for cardiac catheterization prior to surgery.

The physical findings were as follows: There was a prominent systolic thrill over the precordium best felt at the third left intercostal space. The apex was palpable 1 cm. medial to the left midclavicular line and was normal in character. At the pulmonary area there was a continuous murmur beginning after the first sound, Grade 5 intensity during systole and extending over diastole which was Grade 3. The P_2 was normal in intensity. There was a systolic murmur at the apex. No apical presystolic murmur was present. M_1 was normal. The pulses were equal. Blood pressure was 100/60 mm. Hg. The electrocardiogram was normal.

Fluoroscopy and x-rays: Heart was normal in size, shape, and position. Lung vascularity was normal. There was slight fullness of pulmonary artery segment. A diagnosis of an uncomplicated patent ductus arteriosus was made. On operation a medium-sized duct was divided and ligated. All murmurs disappeared after operation.

CASE 2.—(Group A, Type 2), E. L. This 8-year-old child was catheterized in 1951, and was brought back for revaluation because of repeated attacks of upper respiratory tract infection. The mother died during the delivery and was known to have a large P. D. A.

Physical examination revealed a small underdeveloped child. There was a systolic thrill over the precordium, most marked over the second left intercostal space. There was a continuous murmur in the second left intercostal space beginning after the first sound and going into diastole. The systolic murmur at the apex was rough in character. There was also an apical presystolic murmur. M_1 was normal. The pulmonary second sound was louder than the aortic second sound. Blood pressure was 180/70 mm. Hg. Electrocardiogram showed left-heart strain.

Fluoroscopy and x-rays: These revealed an enlarged heart and an elongated left ventricle border. Hilar dance was present, and lung fields were hypervascular. Pulmonary artery was enlarged. There were no encroachments upon the esophagus in either view and a slight posterior displacement of the barium-filled esophagus was found. The data are summarized here.

Catheter Location	*Oxygen Content Vol. %*	*Pressures*
S. V. C.	9.5	
Hepatic Ven.	6.9	
R. A.	9.8	
R. V.	9.7	60/2
M. P. A.	12.4 – 12.3	49/27 M = 37
R. P. A.	11.2	48/25
Femoral artery	13.3 (89% Sat.)	

0_2 consumption = 100 c.c./minute.
Total systemic flow = 3 liters.
Total left ventricular output = 8 liters.
Left-to-right shunt = 5 liters.
62 per cent of the blood was thus shunted through the P. D. A.

CASE 3.—(Group A, Type 2), P. B. This 7-month-old female child had repeated attacks of upper respiratory tract infections and congestive heart failure which responded to antibiotics and digitalis. There was no murmur present at birth. At the age of 3 months a systolic murmur was detected.

Her physical examination on admission revealed an underdeveloped child. There was a systolic thrill over the pulmonary area. There was a continuous murmur at the pulmonary area, which began shortly after the first heart sound. The systolic element of the murmur was Grade 4 in intensity and the diastolic element was Grade 2. Pulmonary second sound was very soft.

There was an apical Grade 4 systolic and a presystolic murmur. M_1 and M_2 were normal. Blood pressure was 110/50-0 mm. Hg. Both femoral pulses were felt. Electrocardiogram showed left-heart strain.

Fluoroscopy and x-ray: The pulmonary vascularity was increased. There was an enlarged pulmonary artery and left ventricle.

Catheterization: The catheter was passed into the aorta via the ductus. During the procedure, the catheter clotted before any samples or pressures were obtained.

The child was operated upon. A large ductus was divided and ligated. All the murmurs disappeared after operation, and the child is now doing very well.

CASE 4.—(Group B, Type 1a), H. E. This was a 35-year-old female known to have some type of heart condition since the age of 3 years. One month prior to admission she had recurrent chills and became dyspneic and orthopneic. Marked pedal edema developed. This attack of congestive heart failure responded well to digitalis.

Physical examination revealed a poorly developed female. The liver was enlarged and tender. There was a systolic thrill over the second left intercostal space. Pulmonary second sound was accentuated and louder than aortic second sound. There was a Grade 4 systolic murmur and a soft early diastolic murmur at the second left intercostal space. Blood pressure was 124/84 mm. Hg. Electrocardiogram showed right-heart strain.

Fluoroscopy and x-ray: Pulmonary arteries were dilated. Aortic knob was fairly promi nent. Moderate enlargement of right ventricle was present.

Catheter Location	*Oxygen Content Vol. %*	*Pressures*
R. P. A.	14.7	85/45
M. P. A.	14.5	M = 60
R. V.	10.8	90/16
R. A.	8.4	M = 7
S. V. C.	10.3	
B. A.	19.4 (95% Sat.)	124/72

0_2 consumption = 190 c.c./minute.
Total pulmonary blood flow = 4.0 liters/minute.
Effective pulmonary blood flow = 2.1 liters/minute.
Left-to-right shunt = 1.9 liters/minute.

CASE 5.—(Group B, Type 2), C. R. This 5½-year-old male child who was underdeveloped had no evidence of cyanosis at birth. At the age of 3 weeks the patient was admitted for pyloric stenosis. This time a murmur was detected, and the heart was found to be enlarged. A corrective operation for pyloric stenosis at that time was undertaken. Following this the child had had repeated attacks of upper respiratory tract infection and sore throats. There had been no history of cyanosis, squatting, or congestive heart failure.

Examination of the cardiovascular system revealed the presence of a systolic thrill over the precordial area. At the pulmonary area there was a Grade 4 systolic murmur which began shortly after the first heart sound. The pulmonary second sound was loud and booming. At the apex there was a Grade 4 systolic murmur and an apical presystolic murmur resembling that heard in mitral stenosis. The pulse was rapid and collapsing. The blood pressure was 110/60 mm. Hg. Electrocardiogram showed combined heart strain.

Fluoroscopy and x-ray: The pulmonary artery was enlarged and there was a hilar dance. On oblique views there appeared to be an enlarged left, as well as a right ventricle. The barium-filled esophagus was displaced to the left and posteriorly.

Catheterization: The catheter was placed in the aorta through what seemed to be a patent ductus. The blood data and pressures are as follows:

Catheter Location		*Oxygen Content Vol. %*	*Pressures*
I. V. C.		13.1	
S. V. C.		11.1	2–4 M = 2
R. A.	High	10.6	
	Low	8.7	
R. V.	Low	10.9	68/0
	High	12.2	
R. P. A.		13.3	68/45 M = 58
L. P. A.		14.3	70/45 M = 60
Ductus area		15.5	95/50 100/55
Aorta		15.8 (97% Sat.)	85/50 M = 75
B. A.		15.6	105/50 M = 75

0_2 consumption = 100 c.c./minute.
Cardiac output was determined.
Systemic flow = 2 liters/minute.
Total pulmonic flow = 5.2 liters/minute, that is about 61% of the left ventricular output shunt into the pulmonary circuit.

There has been no further follow-up on this case.

CASE 6.—(Group B, Type 2), D. D. This was a case of a 6-year-old white female child who was admitted for cardiac catheterization. The mother gave a history of German measles during pregnancy. The child was known to have a heart murmur from birth. There was no history of cyanosis, squatting, or congestive failure. Her tolerance to exercise was diminished.

A physical examination revealed a slender underdeveloped child. There was a precordial bulge and a right ventricular heave. A systolic thrill was present, best felt in the second left intercostal space. There was a systolic and diastolic murmur at the pulmonary area. The Grade 4 systolic murmur began shortly after the first heart sound and continued in early diastole. Pulmonary second sound was greater than the aortic second sound. At the apex a presystolic murmur resembling the one heard in mitral stenosis was present. There was a third sound heard over the apex. Femoral pulses were also palpated. Electrocardiogram showed incomplete right bundle branch system block and right-heart strain.

Fluoroscopy and x-rays: The heart was enlarged mainly to the right, but also to the left. There were increased pulmonary markings and prominent hilar dance. The heart shadow occupied almost the whole screen in oblique views.

Catheterization: The catheter was passed through the pulmonary artery down the aorta. The data were as follows.

Catheter Location		*Oxygen Content Vol. %*	*Pressures*
S. V. C.		8.9	Mean 0 — 1
R. A.	Low	7.4	
	Mid	7.7	
I. V. C.		6.9	
R. V.	High	7.6	70/0 — 95/0
	Mid	8.3	
M. P. A.		12.6	
R. P. A.		11.6 — 13.1	
L. P. A.		11.6	70/30 M — 45
Abdominal aorta		13.7 (96% Sat.)	
B. A.		14.6 (93.6% Sat.)	

0_2 consumption = 100 c.c./minute.
Systemic flow = 1.8 liters/minute.
Total pulmonary flow = 5 liters/minute.
Left-to-right shunt = 3.2 liters/minute = 64 per cent of left ventricular output.

At operation a P. D. A. of a diameter larger than the aorta was divided and ligated. All murmurs disappeared after operation.

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THE ELECTROCARDIOGRAM IN EBSTEIN'S ANOMALY OF THE TRICUSPID VALVE

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A STUDY of the electrocardiograms in eight cases of Ebstein's anomaly of the tricuspid valve illustrated in case reports has revealed a pattern which is sufficiently distinctive to be of diagnostic value. The pattern of the electrocardiogram is described in this paper and the characteristic features have been correlated with the anatomic anomalies found in this condition.

MATERIAL AND METHODS

An analysis of the electrocardiograms in eight cases of Ebstein's anomaly of the tricuspid valve illustrated in case reports was made.[2-7] Only those electrocardiograms which included unipolar chest leads have been included in this report. The majority of electrocardiographic reproductions were sufficiently clear to afford reasonable accuracy in the making of measurements.

Three of the cases of Ebstein's anomaly had been discovered at autopsy[3,5,7] while the diagnosis in the remainder had been made clinically with the aid of cardiac catheterization[2,4,6] or angiocardiography.[4-6]

The amplitude and duration of the various deflections of the electrocardiogram were measured in each of the leads. These measurements were compared with those found in normal subjects.[8,13] Despite the presence of three patients of less than 20 years of age, normal adult standards were used exclusively. The electrical axis of the P wave, QRS complex, and the T wave was measured by the area method of Ashman and associates.[10]

ELECTROCARDIOGRAPHIC FINDINGS

Only those features in the electrocardiogram which were abnormal will be presented. These include abnormalities of the P wave, a prolongation of the P-R interval, a prolongation of the QRS complex and a pattern of right bundle branch block which differs from that usually found (Fig. 1*A*).

Presented in abstract to The Society for Experimental Biology, Johannesburg, and published in South Africa J. Med. Sc. **18**;88-89, 1953.

Received for publication Sept. 21, 1954.

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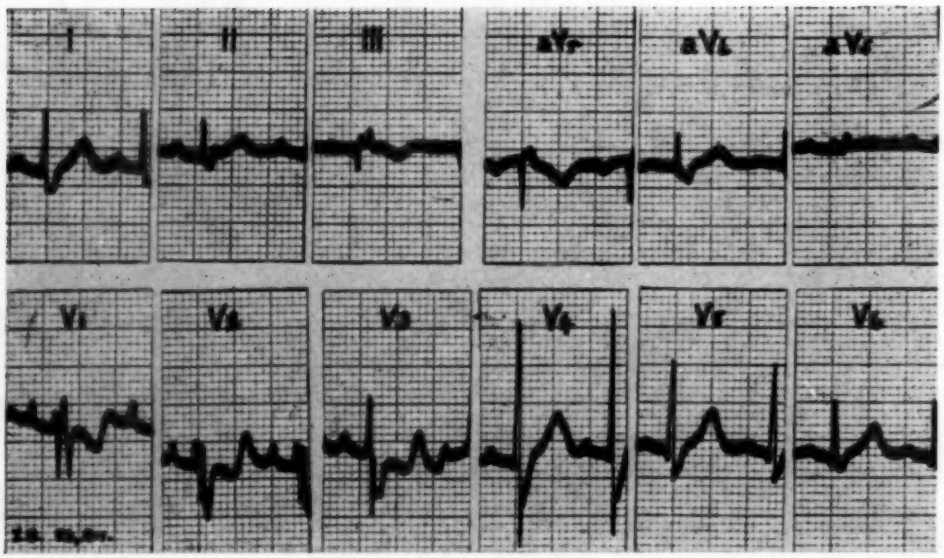

Fig. 1A.—The electrocardiogram of an unpublished case of Ebstein's anomaly showing the characteristic features described in the text. Unlike the cases analyzed in this report incomplete rather than complete right bundle branch block is present.

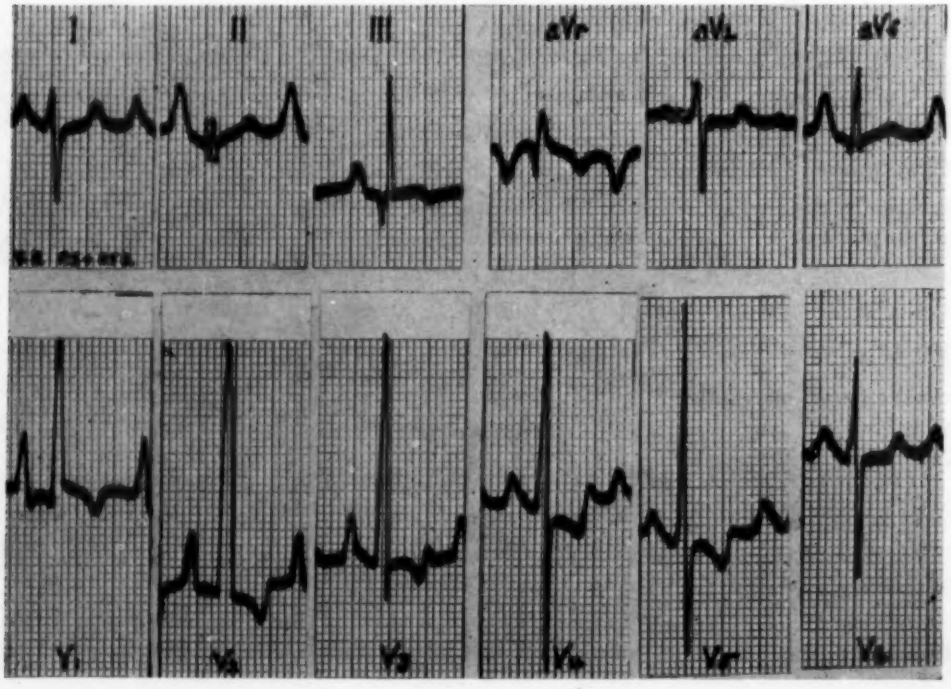

Fig. 1B.—The electrocardiogram of a case of pulmonic valvular stenosis and patent foramen ovale for comparison with that of Ebstein's disease. See text for discussion.

The P waves were abnormal in either amplitude, duration, or both, in all subjects. Tall P waves were present in Leads I, II, V_1, V_2, and V_3 in the majority of cases. The average height of the P wave in Lead II was 2.6 mm. with a range of 1.6 mm. to 4.0 mm. It exceeded the upper limit of normality of 2.5 mm.[9] in four cases. The P wave in the chest leads was greater than 2.0 mm. (the upper limit of normality of Alimurung and associates)[17] in six of the seven cases in which Lead V_2 was recorded. The average duration of the P wave was 0.105 sec. while the upper limit of duration of the normal P wave (0.11 sec.)[9] was exceeded in three cases. Obvious notching was unusual although some showed slurring on the upstroke or on the downstroke and occasionally were flat-topped. In a number of cases the P-Q segment was markedly depressed below the T-P segment.

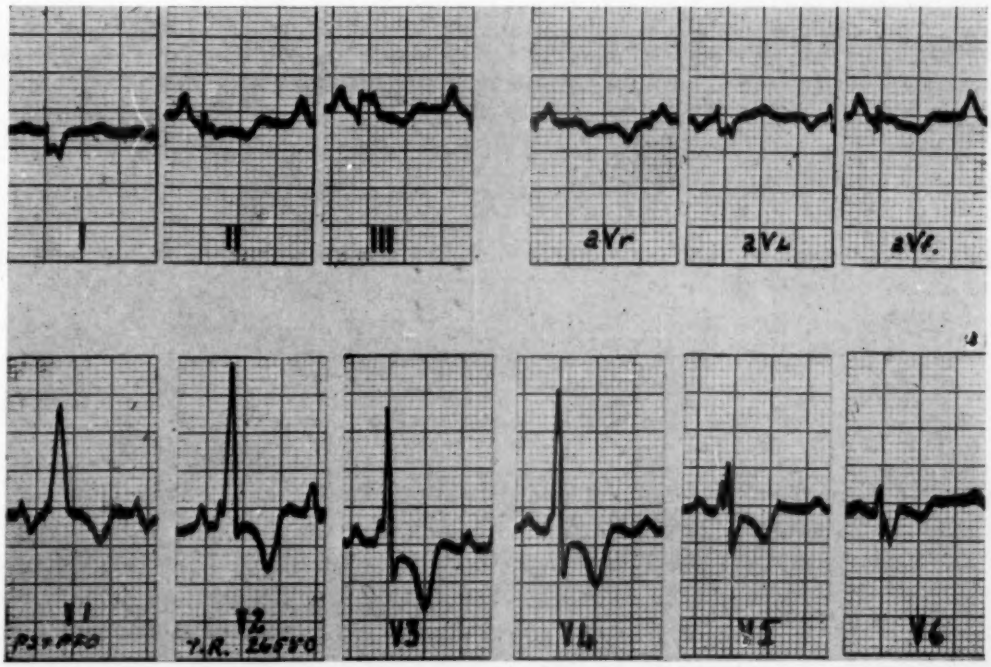

Fig. 1C.—The electrocardiogram of a case with infundibular stenosis and patent foramen ovale for comparison with that of Ebstein's disease. Complete right bundle branch block is present. See text for discussion.

The P-R interval was 0.20 sec. or more in seven of the eight cases. The average duration of the P-R interval was 0.22 sec. with a range of 0.18 sec. to 0.30 sec.

The voltages in all leads were small in a number of records (Table I). The sum of the largest R and S wave in the standard limb leads was less than 5.5 mm. in three cases and less than 10 mm. in five cases. By convention electrocardiograms with the sum of the R and S wave less than 7 mm. in the standard extremity leads have been considered to show low voltage.[10] The voltage of the chest leads was assessed by the sum of the largest R and S wave in each lead and was compared with similar measurements in a normal group of subjects

TABLE I

CASE NO.	REFERENCE	AGE YR.	SEX	AUTOPSY	CATH.	ANGIO.	STANDARD LEADS					AT DEG.	R-WAVE V_1 MM.	R-WAVE V_5 MM.	LARGEST R + S ST. L MM.	R + S V_1 MM.	R + S V_6 MM.
							P-WAVE		P-R SEC.	QRS SEC.	AQRS DEG.						
							SEC.	MM.									
1.	Baker et al.[3]	17	M	+	+	+	.10	3.7	.20	.13	+133	+63	2.0	10.0	18.7	9.5	—
2.	Baker et al.[3]	11	F	+	+	+	.10	4.0	.30	.16	+55	−14	3.0	12.0*	14.5	4.0	13.0
3.	Paul et al.[7]	16	M	+	−	−	.10	3.0	.23	.12	−128	+101	5.0†	11.0	5.5	8.5†	—
4.	Tournaire et al.[2]	39	F	−	+	−	.10	1.6	.24	.16	+125	−31	2.0	4.0	3.5	2.5	7.7
5.	Reynolds[4]	33	F	−	+	+	.11	2.0	.18	.16	−154	+31	6.0	18.0	8.5	13.2	18.0
6.	Soloff et al.[5]	34	F	−	−	+	.12	1.6	.22	.13	+88	−35	1.0	6.0	14.0	3.0	8.0
7.	Van Lingen et al.[6]	20	F	−	+	−	.11	3.0	.20	.12	+167	−15	3.0	10.0	9.4	4.5	20.0
8.	Van Lingen et al.[6]	21	F	−	+	−	.10	2.0	.20	.12	+138	+53	1.6	3.5	4.5	2.6	10.5
		Ave.					.105	2.6	.22	.137			2.9	9.3	9.8	5.9	12.9
		Max.					.12	4.0	.30	.16			6.0	18.0	18.7	13.2	20.0
		Min.					.10	1.6	.18	.12			1.0	3.0	3.5	2.5	7.7

*Leads V_4, V_5, and V_6 inverted in the original reproduction.
†Lead V_2 was measured in the absence of lead V_1.

between the ages of 20 and 30 years.[9] The average of the sum of R and S in Lead V_1 in Ebstein's anomaly was 5.4 mm. against a normal average of 15 mm. Similar measurements in Lead V_2 were 6.2 mm. as compared with 23.5 mm.; in V_3, 7.8 mm. and 22 mm.; in V_4, 10.0 mm. and 20 mm.; in V_5, 10.8 mm. and 13.5 mm.; and V_6, 13.0 mm. and 12.3 mm. Thus, in Ebstein's anomaly there was a tendency for the standard limb leads and precordial leads from V_1 to V_4 to have smaller than normal QRS complexes while Leads V_5 and V_6 were close to average normal in amplitude.

The electrical axis of the heart varied from slight to extreme right-axis deviation ($+90°$ to $-120°$) in six cases.[10] Only two cases fell within the normal range, and these were $+55°$ and $+88°$. The average axis of the P wave was $+40$ with variations from $-22°$ to $+59°$.

Complete right bundle branch block, according to the criteria of Wilson and associates,[11] and a duration of the QRS complex of 0.12 sec. or more was present in all the cases. Other evidence of right bundle branch block was invariably present and included a broad slurred S wave in Lead I and in leads over the left chest, particularly Leads V_5 and V_6. The intrinsicoid deflection in Lead V_1 occurred later than it did in Leads V_5 and V_6. An additional outstanding feature of the bundle branch block in Ebstein's anomaly was the smallness of the R and R′ (secondary R) wave in Lead V_1 and commonly in Leads V_2, V_3, and V_4 as compared with the larger and relatively normal sized R waves in Leads V_5 and V_6 (Fig. 1*A*). The average height of the R wave was 2.6 mm. in V_1; 2.5 mm. in V_2; 5.3 mm. in V_3; 5.9 mm. in V_4; 8.5 mm. in V_5; and 9.9 mm. in V_6. This is in striking contrast to the usual finding in right bundle branch block, particularly when it is complete. In the latter instance there is prominence of R or R′ in Lead V_1 which exceeds the R waves in Leads V_5 and V_6 in amplitude [12] (Fig. 1*C*).

The T waves were variable. In five cases the T-wave axis ($\bar{A}_T$) was approximately in the opposite direction to the QRS axis ($\bar{A}_{QRS}$) while the difference was less marked in the remaining three cases. Diametrically opposite direction of the QRS and T axes is common in complete right bundle branch block. In such cases the T wave is negative in complexes with large R waves and vice versa. On the average the T wave was positive in Lead I and Leads V_5 and V_6 and negative in Lead III and in Leads V_1 and V_2 although this pattern was far from uniform. Diphasic T waves ($- +$) were occasionally seen, being found in Leads V_2 and V_3 in about one-third of the cases.

DISCUSSION

The electrocardiogram in the eight cases of Ebstein's anomaly of the tricuspid valve was characterized by complete right bundle branch block, and by small deflections (R and R + S) in Lead V_1 and commonly in Leads V_2, V_3, and V_4. In addition a large amplitude with increased duration of the P wave and a prolongation of the P-R interval occurred frequently. Right bundle branch block,[1-7] prominence of the P waves, and prolongation of the P-R interval[13] have all been described previously. Supraventricular arrhythmias occurred in only one of the cases in this series but have been reported to be of frequent occurrence.[1,13]

The electrocardiogram in Ebstein's anomaly can be ascribed to the anatomic abnormalities present in this condition. According to Engle and associates[1] the malformation consists of the displacement of the fused leaflets of the tricuspid valve into the body of the right ventricle. This displacement divides the right ventricle into a proximal chamber which is continuous with the right auricle and a distal chamber which includes the outflow tract of the right ventricle. The proximal part of the right ventricle to which the tricuspid valve is adherent is extremely thin and has been considered to be a developmental defect. The wall of the right ventricle distal to the displaced tricuspid valve is of normal thickness. The congenitally thin proximal part of the right ventricle is markedly dilated, and the right auricle shows dilatation and hypertrophy. In the three cases described by Engle and associates[1] the malformed portion of the right ventricle measured only 1 mm. to 2 mm. in thickness but the muscle fibers, which were reduced in number, appeared normal on microscopic examination in two of these cases. In at least three-fourths of the reported cases there has been patency of the foramen ovale,[1] and this was present in all the cases of the present series.

The characteristic feature of the electrocardiogram of Ebstein's anomaly was the small positive deflections (R and R′) in Lead V_1 and commonly in Leads V_2, V_3, and V_4 which were significantly smaller than those in V_5 and V_6. Such a finding is in marked contrast to the pattern of right bundle branch block seen in other types of heart disease where large positive R deflections in Lead V_1 exceed in size the R deflections over the left chest.[11] The size of the R or R′ wave in Lead V_1 in right bundle branch block depends upon the degree of block and the thickness of the right ventricular wall. It is generally taller in complete than in incomplete right bundle branch block,[11] while associated right ventricular hypertrophy causes larger R or R′ waves in Lead V_1 than are found in the absence of hypertrophy.[14] The smallness of the deflections in Leads V_1 to V_4 in Ebstein's anomaly can thus be considered to be due to the thinness of the right ventricular wall. The activation of the septum from left to right and delayed activation of the right ventricle in the usual type of right bundle branch block with a normal or enlarged right ventricle produces large positive deflections in leads facing the right ventricle (V_1, V_2, etc.), and small positive deflections in leads facing the left ventricle (V_5, V_6). This results from the abnormal activation of septum and right ventricle producing sufficiently large voltages to counteract those normally produced by the left ventricle. The reverse of this pattern in the right bundle branch block of Ebstein's anomaly, with small deflections in leads facing the right ventricle, can be attributed to the thinness of the right ventricular wall, and the relatively normal-sized deflections in Leads V_5 and V_6 can be accounted for by left ventricular effects which are little influenced by the small potentials produced by the thin right ventricle.

Additional evidence for the assumption that the smallness of the R waves in Leads V_1, V_2, V_3, and V_4 in Ebstein's anomaly is due to the thinness of the right ventricular wall is both direct and indirect. The size of deflections in any lead depends upon the closeness of that lead to the ventricular muscle, the thickness of the muscle, and the direction in which the electromotive force is directed

in regard to the lead. Craib[33] demonstrated that the size of a deflection varies as the square of its distance from the heart. In addition the deflections in leads recorded directly on heart muscle are many times greater than those recorded at some distance away over the chest. In Ebstein's anomaly the deflections over the right ventricle remain small despite the dilatation of the right ventricle and its intimate contact with the anterior chest wall. Secondly, the thickness of the muscle underlying an electrode influences the size of deflections in the electrocardiogram. The greater size of R waves in leads facing the left ventricle as compared with those occurring over the right ventricle in the normal precordial electrocardiogram has been attributed to the greater bulk of the left ventricle.[11] Low voltages of deflections have been found in cases showing extensive myocardial fibrosis,[13] and they may be completely absent in myocardial infarction.[11] The muscle fibers in the proximal chamber of the right ventricle in Ebstein's anomaly have been shown to be normal in appearance but reduced in number.[1] The thinness and paucity of muscle fibers of the right ventricle in Ebstein's anomaly would therefore appear to account for the small deflections recorded over the right ventricle. Finally, the direction of spread of the electromotive force in the usual type of right bundle branch block is largely parallel to the plane of right chest Leads V_1 and V_{3R} and under such circumstances produces large R waves in those leads. However, the R waves over the right chest leads are small in Ebstein's anomaly despite the presence of right bundle branch block.

The smallness of the voltages of the limb and chest leads was a feature of some but not all the cases and is not considered to be characteristic except in Leads V_1 to V_4. Although the thinness of the right ventricular wall can be considered to be responsible for the changes in the chest leads, additional factors are necessary to explain the generalized reduction of the deflections seen in all leads in some of these cases. However, no clinical or autopsy evidence of a poor conducting medium such as edema, pericardial fluid, emphysema, etc., was found to account for the low voltage, although it is possible that the large blood volume of the greatly dilated heart may be important in this regard.[13]

The abnormalities of the P wave (increase in amplitude and duration) can be ascribed to hypertrophy and dilatation of the right auricle. A number of cases showed gross depression of the P-Q segment which would represent an increase in the forces of repolarization of the large auricle. The increase in the P-R interval is at least partially attributable to the prolongation of the P wave. The average duration of the P wave was 0.105 sec., while the average in normal adults is 0.08 sec.[8] If the difference between the duration of the P wave found and that present in normal subjects is subtracted from the average P-R interval in cases of Ebstein's anomaly, then the P-R interval is reduced from 0.22 sec. to 0.19 sec., which is within normal limits. The large positive P waves in Lead V_2 and less commonly in Leads V_1 and V_3 in Ebstein's anomaly are due to right auricular hypertrophy and dilatation. These P waves differ from those of left auricular enlargement, sometimes seen in mitral stenosis, which tend to have notching, a left-axis deviation of the P wave in the standard limb leads,

and a diphasic (+ −) complex with a broad, rounded negative or terminal component in Lead V_1. While right auricular enlargement may cause diphasic P waves in Lead V_1, these generally show a sharp positive and negative component.

The incidence of complete right bundle branch block in congenital heart disease is relatively uncommon.[7,12,28-30] It has, however, been described in a large variety of conditions. It is almost constantly found in Ebstein's anomaly and not infrequently in pulmonic stenosis with intact ventricular septum.[16,18-24] It has been described, but is not a common finding in atrial septal defects,[7,25,32] Eisenmenger's complex,[24] and coarctation complicated by patent ductus arteriosus.[26,27] With the exception of Ebstein's anomaly, complete right bundle branch block and persistent incomplete right bundle branch block are almost invariably associated with right ventricular hypertrophy and dilatation in the younger age groups and show large positive deflections in the right chest leads.

In the absence of large positive deflections in the right chest leads of the electrocardiogram it is possible to confuse incomplete or complete right bundle branch block of other congenital anomalies with that of Ebstein's anomaly. However, with the exception of tricuspid atresia and its distinctive electrocardiogram, it is found that right atrial hypertrophy is clearly associated with right ventricular hypertrophy in congenital heart anomalies (unpublished observations). It follows that congenital heart disease showing evidence of right bundle branch block without evidence of right ventricular hypertrophy (large positive deflections in the right chest leads) will not be associated with electrocardiographic evidence of right atrial hypertrophy and dilatation. In Ebstein's disease it is the rule rather than the exception to find electrocardiographic evidence of right atrial hypertrophy in the absence of evidence of right ventricular hypertrophy. The association of electrocardiographic evidence of right ventricular dilatation (right bundle branch block), absence of evidence of right ventricular hypertrophy (small positive deflections in the right chest leads) and evidence of right atrial hypertrophy and dilatation (large P waves in the right chest leads) would appear to be a distinctive characteristic of the electrocardiogram of Ebstein's disease.

The electrocardiogram of Ebstein's anomaly is of greatest value in the differentiation of this anomaly from some cases of pulmonic stenosis with intact ventricular septum which can give a clinical and radiological picture which closely resembles that of Ebstein's anomaly.[1] The electrocardiogram in these cases of pulmonic stenosis with intact ventricular septum and gross dilatation and hypertrophy of the right ventricle shows large positive deflections in Leads V_1 which may extend to V_4 or even beyond.[16] The large size of these deflections reflects the thickness of the right ventricular wall and differs from the small deflections in Leads V_1 to V_4 found over the thin right ventricle of Ebstein's anomaly (Figs. 1*A*, 1*B*, and 1*C*).

While complete right bundle branch block has characterized the eight cases presented in this report, it is likely that this feature is dependent upon dilatation of the right ventricle. Serial sections of the conduction system of

the heart in one case have failed to reveal any defect.[34] It follows that right bundle branch block may be absent in cases of Ebstein's disease which do not show right ventricular dilatation. On the other hand small deflections over the right chest leads will be present in all cases because of the thinness of the wall of the proximal part of the right ventricle in this anomaly. In support of this contention an example of incomplete right bundle branch block in an unpublished case of Ebstein's anomaly has been demonstrated in Fig. 1*A*. This case has not been included in those analyzed in this report.

SUMMARY

1. The electrocardiograms of eight cases of Ebstein's anomaly of the tricuspid valve have been studied. These were characterized by complete right bundle branch block in all cases, and by small deflections (R, R′, and R + S) in Leads V_1 and commonly in Leads V_2, V_3, and V_4. Tall and prolonged P waves occurred commonly and were considered to be evidence of right auricular hypertrophy and dilatation. Prolongation of the P-R interval and supraventricular tachycardia were also observed.

2. It was considered that the small deflections of the QRS complex in the right chest leads were due to the thinness of the proximal chamber of the right ventricle which is a characteristic and constant feature of Ebstein's disease. This feature of the electrocardiogram in Ebstein's anomaly is only rarely found in complete or incomplete right bundle branch block from other causes and is considered to be of value in the diagnosis of this condition.

3. The association of electrocardiographic evidence of right atrial hypertrophy in the absence of evidence of right ventricular hypertrophy (small R or R′ waves in the right chest leads) is uncommon in other types of congenital heart disease and is a characteristic feature of Ebstein's anomaly.

SUMMARIO IN INTERLINGUA

1. Esseva studiate le electrocardiogrammas de octo casos del anomalia de Ebstein del valvula tricuspide. Illos esseva characterisate per complete bloco del branca dextere in omne casos e per parve deflexiones (R, R′, e R + S) in le derivationes V_1 e communmente V_{2-4}. Alte e prolongate undas P occurreva communmente e esseva considerate como evidentia de hypertrophia e dilatation dexteroauricular. Esseva etiam observate prolongation del intervallo P-R e tachycardia supraventricular.

2. Nos opina que le parve deflexiones del complexo QRS in le derivationes dexterothoracic esseva le resultato del tenuitate del camera proximal del ventriculo dextere, lo que es un constante characteristica del morbo de Ebstein. Iste aspecto del electrocardiogramma in casos del anomalia de Ebstein se trova solo rarmente in complete o incomplete bloco del branca dextere causate per altere conditiones e ergo pare esser de valor diagnostic.

3. Le presentia de signos electrocardiographic de hypertrophia dexteroatrial associate con un absentia de signos electrocardiographic de hypertrophia dexteroventricular—parve undas R o R′ in derivationes dexterothoracic—es

un characteristica del anomalia de Ebstein e occurre rarmente in altere typos de cardiopathia congenite.

Dr. T. H. Bothwell kindly helped in the preparation of this paper. Mr. A. M. Shevitz is responsible for the photographic reproduction.

ADDENDUM

A number of additional reports of Ebstein's anomaly of the tricuspid valve have appeared since the completion of this study and the electrocardiograms substantiate the findings presented in this communication.

Goodwin and others: Am. Heart J. **45**:144, 1953.
Broadbent and others: Proc. Mayo Clin. **28**:79, 1953.
Henderson and others: Brit. Heart J. **15**:360, 1953.
Mead and others: Thorax **9**:14, 1954.

One case presented by Graux and Merlen (Arch. mal. coeur **44**:263, 1951) showed an atypical left bundle branch block. This occurred in a patient of 72 years of age with little dilatation of the right ventricle, and it is likely that the left bundle branch block was produced by atherosclerosis and myocardial ischemia.

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THE AURICULAR T WAVE AND ITS CORRELATION TO THE CARDIAC RATE AND TO THE P WAVE

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ALTHOUGH the auricular T wave (T_a) was recognized and designated by Hering[1] as early as 1912, our knowledge concerning this wave still remains incomplete and lacks precision. By definition it represents the recovery period of the activity of the auricular musculature or in the electrophysiologic sense it indicates the repolarization that follows the depolarization of the auricular musculature. Nevertheless, morphologic particularities and unusual situations still cause much perplexity. The electrical activity of the auricular musculature is represented in the electrocardiogram by 3 components; (1) the P wave, which indicates the onset of invasion of the excitation within the auricular musculature; (2) the P-T_a segment, extending from the end of the P wave to the beginning of the T_a wave, a period where there exists balanced activity or temporary neutralization of potential differences; (3) the T_a wave, a small negative deflection, corresponding to the recovery period or to the retreat of electrical activity. While the P wave is always clearly visible, the auricular T wave, a few pathologic conditions excepted, is always invisible, and the P-T_a segment is accessible to direct observation only in its initial portion. The auricular T wave is practically always unrecognizable, because it coincides with the activation of the ventricular musculature and thus it merges with the graphic elements of the ventricular complex. On the other hand, the exact duration of the P-T_a segment cannot be determined because the beginning of the T_a wave is invisible. What can be actually observed in normal and in most pathologic cases in respect to the auricular T wave is the change of the initial section of the P-T_a segment. This consists in the displacement of its level, but neither its duration nor any other alterations of the T_a wave can be determined accurately. All measurements and observations concerning durations of the P-T_a interval and changes of the T_a wave have been performed in cases of complete heart blocks, marked auriculoventricular conduction disturbances, and in auricular extrasystoles where the auricular complex is not immediately followed by a ventricular complex, and so all three components can thus eventually be examined. Such studies were carried out either in the limb leads or in the esophageal electrocardiogram, which proved to be especially suitable for this purpose.

Received for publication Nov. 5, 1954.

The scanty data regarding incidence and magnitude of the auricular T wave, as expressed by the displacement of the P-R interval, to be found in the literature are rather incomplete. Shipley and Hallaran[2] state that in 200 normal electrocardiograms they have observed slight displacement of the P-R interval attributable to the presence of an auricular T wave in 95 per cent of the cases in one or more leads. The maximum depression measured 0.8 mm. in Lead II. Stewart and Manning[3] in reviewing the electrocardiograms of 500 healthy aviators declare that a slight depression of the P-R segment designated as the T_a wave was common, but it exceeded 0.5 mm. in only nine records. Zuckerman and collaborators[4] give standard values for the height of the T_a wave as follows: minimum, 0; medium, 0.25 mm.; and maximum 0.5 mm. The duration of the P-T_a interval is estimated by different authorities to be of variable length. Eiger[5] indicates 0.25 to 0.80 sec.; Boden and Neukirch,[6] 0.40 to 0.52 sec.; Sprague and White,[7] 0.34 to 0.42 sec.; Brown,[8] 0.405 to 0.503 sec.; Enselberg,[9] 0.22 to 0.50 sec.; Pardee,[10] 0.30 to 0.40 sec.; and finally Katz,[11] 0.35 sec.

The present paper reports a systematic investigation of the factors and correlations that govern alterations of the P-T_a segment, the only visible section of the T_a complex in the normal electrocardiogram. As a result, many confusing details have been clarified and various quantitative correlations established.

METHOD

Displacement of the P-R interval was measured by comparing the position of this segment with that of the T-P interval, i.e., measuring the distance between the upper level of the T-P interval and the upper level of the P-R interval expressed in millimeters. The average of several measurements was taken. The minimum visible displacement was considered as low as 0.2 mm. In spite of efforts to make measurements as accurate as possible, the fact that most distances were of an order smaller than 1 mm., introduced a subjective cause of error. Therefore, measurement of the displacement of the P-T_a segment can be considered as only approximately correct. To obtain more significant figures, average values were calculated whenever possible.

Displacement of the P-T_a segment was measured in the second lead only, as there the P wave is tallest. In addition, in every record, height and surface area of the P wave were determined and expressed in millimeters and microvolt-seconds (m.v.s.), respectively. The length of the cardiac cycle was determined by calculating the average length of several successive R-R intervals. A total of 210 records of healthy males and females were examined, and were divided into groups of thirty, according to cardiac rates ranging from 51 to 120 beats per minute.

RESULTS

Correlation Between the Displacement of the P-T_a segment and the Cardiac Rate.—Two positive correlations could be clearly established between the incidence and the degree of displacement of the P-T_a segment and the cardiac rate,

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RESULTS

Correlation Between the Displacement of the P-T_a segment and the Cardiac Rate.—Two positive correlations could be clearly established between the incidence and the degree of displacement of the P-T_a segment and the cardiac rate,

Incidence (Table I) of the Displacement of the P-T_a Segment and the Cardiac Rate.—Displacement of the P-R interval was observed at cardiac rates from 51 to 70 beats per minute in two instances out of thirty (6.7 per cent). In the zone of frequencies from 71 to 80, the incidence of a visible P-T_a segment increases abruptly; it was present in eighteen cases (60 per cent) and from 81 to 90 in twenty-two cases (73.3 per cent). At high cardiac rates (91 to 120), displacement was noted in practically 100 per cent of the cases. Therefore, it appears that displacement of the P-R interval entailing a visible P-T_a segment is a function of the cardiac rate. It is absent in practically 100 per cent of the cases with cardiac rates under 70 per minute, and it is present in practically 100 per cent of the cases with rates above 90. In the middle zone of the cardiac rates (71 to 90), the P-T_a segment is increasingly visible and is found in about two-thirds of these cases.

TABLE I. INCIDENCE AND DEPTH OF THE P-T_a SEGMENT AND THEIR RELATIONS TO THE CARDIAC RATE

CARDIAC RATE (MIN.)	P-T_a SEGMENT			
	INCIDENCE		DISPLACEMENT	
	NO. OF CASES	(%)	MEAN	RANGE (MM,)
51–60	2	6.7	0	0 –0.2
61–70	2	6.7	0	0 –0.2
71–80	18	60.0	0.15	0.2–0.4
81–90	22	73.3	0.23	0.2–0.7
91–100	30	100.0	0.54	0.2–1.2
101–110	29	96.7	0.46	0.2–1.0
111–120	30	100.0	0.53	0.2–1.0

Depth of the Displacement of the P-R Interval and the Cardiac Rate.—In each group of cardiac frequencies the average displacement was measured. Table I shows that displacement could not be observed at rates ranging from 51 to 70; from 71 to 80 the average displacement amounted to 0.15 mm.; from 81 to 90 it averaged 0.23 mm. At high rates (from 91 to 120) the average displacement was practically identical: 0.54 to 0.46 to 0.53 mm., respectively, and with an identical range varying from 0.2 to 1.2 mm. Therefore, the depth of the P-T_a segment or the degree of the displacement of the P-R interval shows a direct correlation with the cardiac rate, exhibiting the smallest displacement at low cardiac rates and gradually deepening when these increase. Nevertheless, at high cardiac rates (from 91 to 120 per minute) its depth remains stationary at its highest numerical value.

Correlation Between the P-T_a Segment and the P Wave.—

Height (Table II) of the P wave and the P-T_a segment: Observations were divided according to the height of the P wave into groups with increasing height of 0.4 mm. from 0 to 2.0 mm. In each group of P waves with different height,

incidence and the average displacement of the P-R interval were determined. A definite correlation could be established between the height of the P wave, the incidence and the depth of the P-T_a segment.

TABLE II. THE CORRELATION BETWEEN THE HEIGHT OF THE P WAVE AND THE INCIDENCE AND DEPTH OF THE P-T_a SEGMENT

HEIGHT OF P_2 (MM.)	NO. OF CASES	P-T_a SEGMENT		
		INCIDENCE		DISPLACEMENT (MM.)
		NO. OF CASES	(%)	
0 –0.4	6	2	33.0	0.06
0.5–0.8	27	9	33.0	0.10
0.9–1.2	103	65	63.1	0.275
1.3–1.6	54	40	74.1	0.355
1.7–2.0	20	16	80.0	0.365

Incidence: In the group of records with lowest P wave presenting a height from 0 to 0.4 mm. the incidence of a visible P-T_a segment was 33 per cent. An equal incidence was encountered in the next group of records with a height from 0.5 to 0.8 mm. With increasing height of the P wave, the incidence of a visible P-T_a segment increased and gradually reached its highest value of 80 per cent in the group of P waves with heights from 1.7 to 2.0 mm. Thus, it can be concluded that the incidence of a visible P-T_a segment is directly proportional to the height of the P wave.

Depth of the P-T_a segment: In each group of P waves divided according to height the average depth of the P-T_a segment was determined. The depth of the P-T_a segment was found to be directly proportional to the height of the P wave. In the group with lowest P wave with height varying from 0 to 0.4 mm. the average calculated depth was 0.06 mm. As the height of the P wave increased, the P-T_a segment deepened to a maximum average depth of 0.365 mm. in the group with P waves ranging from 1.7 to 2.0 mm. Therefore, displacement of the P-R interval, i.e., the depth of the P-T_a segment is directly proportional to the height of the P wave.

The dependence of the depth of the P-T_a segment upon the height of the P wave is more pronounced than that of its incidence. Let us consider the incidence 33 per cent and the average depth 0.06 mm. corresponding to the lowest group of P waves as 100, then the relative increase of the incidence of the P-T_a segment in the group of largest P waves, which is 80 per cent, represents 142 per cent, whereas the average depth amounting to 0.365 mm. reveals a relative increase of 500 per cent.

Correlation Between the Surface Area of the P Wave and the Incidence (Table III) and Depth of the P-T_a Segment.—The records were divided, according to the magnitude of the surface area of the P wave, into groups with increasing dimensions. In each group the incidence and average depth of the P-T_a segment were determined. The incidence of the P-T_a segment presented a definite

correlation with the surface area of the P wave. In the group of smallest P waves surface area—measuring from 0 to 2.0 m.v.s.—the incidence amounted to 37.5 per cent. The incidence increased successively with increasing surface area and reached its maximum value of 87 per cent in the group where the surface area of the P wave was the greatest, over 9.0 m.v.s.

TABLE III. THE CORRELATION BETWEEN THE SURFACE AREA OF THE P WAVE AND THE INCIDENCE AND DEPTH OF THE P-T_a SEGMENT

SURFACE AREA OF P_2 (M.V.S.)	NO. OF CASES	P-T_a SEGMENT		
		INCIDENCE		DISPLACEMENT (MM.)
		NO. OF CASES	(%)	
0 –2.0	8	3	37.5	0.10
3.0–4.0	43	20	46.5	0.174
5.0–6.0	95	59	62.1	0.270
7.0–8.0	41	35	85.4	0.400
9.0–	23	20	87.0	0.408

Similar behavior was found with regard to the correlation between the surface area of the P wave and the depth of the P-T_a segment. Thus, the average depth of the P-T_a segment measured 0.1 mm. in the group with the smallest surface area. Displacement of the P-R interval increased progressively with increasing surface area of the P wave, attaining its greatest average depth 0.408 mm. in the group with the largest surface area. To calculate the relative dependence of the incidence and that of the depth of the P-T_a segment on the surface area of the P wave, the corresponding values were compared at the lowest and highest dimensions of the surface area. The result was as follows: incidence increased 132 per cent and depth of the P-T_a segment 308 per cent.

Correlation Between the Minute-Surface Area of the P Wave and the Incidence (Table IV) and Depth of the P-T_a Segment.—As definite correlation could be established between the incidence and the depth of the P-T_a segment, and the cardiac rate and the surface area of the P wave separately, the possibility of other correlations when both determining factors are combined in a single expression was examined. The product formed by the surface area of a single P wave multiplied by the cardiac rate constitutes the minute surface area of the P wave.

Incidence: No record with minute surface area less than 100 m.v.s. was observed. In the groups from 101 to 400 m.v.s. incidence was roughly 23 per cent. The minute surface area of 400 has a special significance. From this value on, the incidence of a visible P-T_a segment increases abruptly. In fact, whereas in the group immediately below 400, i.e., from 301 to 400 the incidence observed was 18 per cent, in the following group from 401 to 500 the incidence registered was 64 per cent. Therefore, 400 in the scale of minute surface area may be designated as the lower threshold level of the P-T_a segment. From 501 up to 800 the incidence remains at nearly the same level of 80 per cent. The numerical value 800 of the minute surface area again has a specific significance.

TABLE IV. THE CORRELATION BETWEEN THE MINUTE-SURFACE AREA OF THE P WAVE AND THE INCIDENCE AND DEPTH OF THE P-T_a SEGMENT

MINUTE-SURFACE AREA OF P_2 (M.V.S.)	NO. OF CASES	P-T_a SEGMENT		
		INCIDENCE		DISPLACEMENT (MM.)
		NO. OF CASES	(%)	
0–100	0	0	0	0
101–200	11	3	27.0	0.07
201–300	26	6	23.0	0.05
301–400	28	5	18.0	0.06
401–500	44	28	64.0	0.24
501–600	44	38	86.0	0.35
601–700	25	22	88.0	0.50
701–800	11	8	73.0	0.48
801–900	5	5	100.0	0.40
901–1000	6	6	100.0	0.50
1001–1100	8	8	100.0	0.51
1101–1200	2	2	100.0	0.55

Above this value the P-T_a segment is constantly visible. Therefore, 800 is designated as the upper threshold level of the P-T_a segment. In conclusion, it can be stated that the minute surface area of the P wave presents a definite correlation with the incidence of the P-T_a segment. The P-T_a segment rarely (23 per cent) appears below the lower threshold level of 400, but it is present in 100 per cent at and over the upper threshold level of 800. In the intermediate zone from 401 to 800, its incidence varies from 64 to 88 per cent. No P-T_a segment was visible below 100.

Depth of the P-T_a segment: Displacement of the P-R interval exhibits a tendency rather than an exact numerical parallelism with the minute surface area of the P wave. With minute surface areas of 101 to 200 m.v.s. the average depth of the P-T_a segment reached 0.07 mm.; this increased to 0.35 mm. at 501 to 600 m.v.s. and attained a maximum value of 0.55 mm. at minute surface areas of 1,101 to 1,200 m.v.s.

Correlation Between Age of Subjects and Incidence and Depth of the P-T_a Segment.—Records were classified according to the age of individuals examined in groups by decades ranging from 11 to 70 years. Incidence and average depth of the P-T_a segment were determined in each group. As a conclusion there could not be established any consistent correlation between the age of the subjects and incidence and displacement of the P-T_a segment.

Clinical Correlations (Table V).—The P-T_a segment was studied in those clinical conditions where the P wave is usually enlarged; such as in cases of mitral valvular diseases, in chronic cor pulmonale, etc. In each group, ten typical cases were selected and corresponding average values were determined.

TABLE V. CLINICAL CORRELATIONS

	AGE (YR.)	CARDIAC RATE (MIN.)	P_2		P_2 SURF. AREA (M.V.S.)	P_2 MIN. SURF. AREA (M.V.S.)	DISPLACEMENT (MM.)
			HEIGHT (MM.)	DURAT. (SEC.)			
Mitral valv. diseases	33.5	92	2.12	0.129	13.15	1230	0.89
Pulmonary patients	57.5	89	1.73	0.107	9.2	825	0.74

Mitral valvular disease: The average age of patients was 33.5 years. Average heart rate: 92 per minute. The P wave showed an average height of 2.12 mm., which is 77 per cent taller than the corresponding normal value. Duration of the P wave measured 0.129 sec. The average surface area of the P wave was 13.15 m.v.s.—119 per cent larger than in normal cases. The minute surface area averaged 1,230 m.v.s. representing an increase of 130 per cent over the corresponding normal value. Depth of the P-T_a segment averaged 0.89 mm. (range 0.5 to 1.5 mm.), i.e., 88 per cent more than in normal cases.

Pulmonary patients: The average age (57.5 years) of these patients was significantly higher than in the previous group. The cardiac rate averaged 89 beats per minute. The P wave was lower and shorter than that of the mitral patients, presenting an average height of 1.73 mm., 44 per cent higher than corresponding normal value, and an average duration of 0.107 sec. The surface area of the P wave measured 9.2 m.v.s., which is 58 per cent greater than in normal cases, and the minute surface area of the P wave averaged 825 m.v.s., which is 63 per cent greater than in normal cases. Average depth of the P-T_a segment was 0.74 mm. (range 0.4 to 1.4 mm.), which is 48 per cent greater than in normal cases at the same cardiac rate. Average values of the surface and minute surface areas of the P wave in these cases were 70 per cent and 67 per cent less than corresponding values in mitral patients.

Consequently, the fundamental correlations established in healthy individuals have been found valid in the clinical field. Depth of the P-T_a segment was more pronounced in that group of patients where the two fundamental determining factors, i.e., cardiac rate and surface area, presented their greatest values.

DISCUSSION

Many reasons explain the unsatisfactory state of knowledge concerning the auricular T wave. Its size is tiny, and it is normally hidden among the graphic elements of the ventricular complex; thus, it cannot be distinguished. The three elements of the auricular complex, i.e., the P wave, the P-T_a segment, and the T_a wave are visible in pathologic conditions only where the P wave is not followed immediately by the ventricular complex, such as occurs in cases with marked disturbances of the auriculoventricular conduction, complete auriculoventricular block, and in auricular extrasystoles. The only visible

section of the auricular T complex is the P-T_a segment which occupies a part of the P-R interval and reveals its presence by a slight depression when the level of the P-R interval is compared with that of the T-P interval. Displacement of the P-R interval is generally small, representing only a fraction of a millimeter and, according to experiences published, can be found in normal cases inconstantly and infrequently. As a matter of fact, the clinical and experimental aspects of the auricular T wave have attracted more interest than its physiologic properties. The fundamental determining factors and their correlations have not yet been exactly established.

To mention only some outstanding features, Abramson and associates[12] have studied the effect of traumatization of the auricular wall on the displacement of the P-T_a segment which was consistently observed in the limb leads. When the left auricle was the site of the injury, P-T_a segment became elevated, whereas in case of the injury of the right auricle P-T_a segment appeared depressed. In Leads II and III the P-T_a segment assumed a depressed position regardless of which auricle was traumatized. Cushing and associates,[13] Langendorf,[14] Hellerstein,[15] and Miller and Perelman[16] have studied the changes of the P-T_a segment and those of the T_a wave in cases of auricular infarction, establishing correlations between the localization of the infarct and the changes registered in the different leads.

Sprague and White[7] in thirty-seven patients with complete heart block have made classical observations concerning the T_a wave which was observed in eighteen instances. Brown[8] and Enselberg[9] have selected the esophageal electrocardiogram for the study of atrial activity and have made important contributions concerning the duration of the recovery period of the auricular complex. Battro and Bidoggia[17] by means of cardiac catheterization have studied the electrocardiographic aspects of the auricular complex.

In normal cases most of the authorities conform with mere description of the inconstantly observed displacement of the P-R interval; quantitative data are rare. Scherf and Boyd[18] state that the P-Q distance frequently lies below the isoelectric line due to the after-deflection of the P wave. Katz[11] declares that the T_a wave may normally cause as much as 1 mm. depression below the isoelectric level of the segment between the end of the P wave and the beginning of the QRS group. Goldberger[19] mentions that the broad swallow wave following P is called the auricular T wave. In a like manner, Pardee[10] states that the auricular T wave is responsible for the difference between the level of the base line preceding P and that of the interval between the ending of P and beginning of the QRS group. Kossmann[20] in his summary concerning the normal electrocardiogram does not discuss the physiologic aspects of the T_a wave. Shipley and Hallaran[2] in reviewing the electrocardiogram of 200 normal adults state that a slight depression of the P-R level below the isoelectric line was observed in 95 per cent of the records. The maximum depression of 0.8 mm. was found in Lead II in 90 per cent of the cases. Different observations are reported by Stewart and Manning,[3] who found in 500 aviators a slight depression of the P-R segment—a common feature—but only observed displacements greater than 0.5 mm. in nine cases. In six cases this occurred in all the three leads and in Lead II only in three instances.

The present study, with its definite results, clarifies many confusing aspects of the P-T_a segment. First of all, it could be established that its presence is conditioned mainly by the cardiac rate. As far as the incidence of the P-T_a segment is concerned there could be recognized two critical cardiac frequencies. No P-T_a segment is visible practically below a cardiac rate of 70 beats per minute. Above 90 contractions per minute, the P-T_a segment is nearly always present in a visible form. In the zone of cardiac frequencies ranging from 71 to 90 beats per minute, the P-T_a segment becomes increasingly visible with an incidence of 60 to 73.3 per cent. Routine electrocardiographic examination is usually carried out after a short period of rest which slows the pulse rate. It follows that most of the healthy individuals examined present such a slow cardiac rate that, according to experiences observed in the present study, the P-T_a is absent or it is rarely visible. This may explain the contradictory results obtained by different authors. Thus, Graybiel and associates[21] in analyzing the electrocardiograms of 1,000 young healthy aviators found an average cardiac rate of 63.8 per minute. According to the histogram published, illustrating the range and distribution of cardiac rates, the major part of the observations belong to that zone of cardiac frequencies where P-T_a segment is not visible. Therefore, it should be borne in mind that the incidence of the P-T_a segment varies with the cardiac rate and cannot be treated in general terms, without reference to the actual cardiac rate, in a manner similar to the length of the Q-T interval. On the other hand, the cardiac rate is not only decisive for the incidence but also for the degree of the displacement of the P-T_a segment. Since it could be established that the depth of the P-T_a segment increases with increasing cardiac rates, therefore published data concerning the degree of displacement of the P-R interval without indicating corresponding cardiac rates may present significant differences. In the present study, the average depth of the P-T_a segment was found to be as low as 0.23 mm. (range from 0 to 1.2 mm.) within normal cardiac rates ranging from 60 to 100. This result agrees closely with data published by Zuckerman and associates,[4] who set for the displacement of the P-T_a segment in normal records a mean value of 0.25 mm. and a maximum of 0.5 mm. Katz[11] fixes for the maximum displacement a value as high as 1 mm. However, neither of these authors mentions the cardiac rate at which their measurements were taken.

Another essential factor that determines the presence and depth of the P-T_a segment is the P wave. The average height of the P wave in the present investigation was 1.19 mm., similar to those established by Ashman and Hull[22] of 1.25 mm., and by Kossmann[20] of 1.07 mm. The height of the P wave itself depends directly on the cardiac rate, a fact demonstrated by measuring the average height in each group of cardiac rates. When the records were classed according to the height of the P wave, a definite correlation could be established between the incidence and the depth of the P-T_a segment and the height of the P wave. With increasing height of the P wave, the incidence and depth of the P-T_a segment increase. When expressed in percentage the correlation between the height of the P wave and the depth of the P-T_a is more pronounced than the correlation between the height and the incidence.

The correlation between the surface area of the P wave and the P-T_a segment was next examined. Surface area was determined according to a method described by Ashman and Byer[23] and expressed in micro-volt-seconds (m.v.s.). Mean surface area of the P wave in the second lead was found to be as large as 5.7 m.v.s. with a minimum of 0.6 m.v.s. and a maximum of 11.0 m.v.s. The magnitude of the mean surface area of the P wave found in the present investigation agrees with the result of the measurements of Novelo,[24] who found 5.0 m.v.s. for the same factor. Larger average surface areas of the P waves could be found when cardiac rates increased. Thus, surface area averaged in the group with cardiac rates of 51 to 60—4.0 m.v.s.; from 61 to 80—5.7 m.v.s.; in the group 81 to 90 showed an average of 6.0 m.v.s., from 91 to 110—5.8 m.v.s., and finally in the group with the highest cardiac rates from 111 to 120, average surface area of the P wave presented its largest value 7.0 m.v.s. The incidence and the depth of the P-T_a segment presented a definite parallelism with the surface area of the P wave. In the group of smallest surface area from 0 to 2.0 m.v.s. the incidence and the depth of the P-T_a segment presented their lowest values of 37.5 per cent and 0.1 mm., respectively. Increasing surface area gradually increases both the incidence and the depth of the P-T_a segment which reach their maximum values of 87 per cent and 0.408 mm. in the group with the largest surface area over 9.0 m.v.s. Relative increase of the displacement was greater than that of the incidence; while depth of the P-T_a segment increased 308 per cent, the incidence increased only 132 per cent, when the two values were compared at the lowest and highest dimensions of the surface area of the P wave.

The present study showed that the incidence and the degree of displacement of the P-T_a segment exhibit two independent correlations, both with the cardiac rate and the surface area of the P wave. These correlations are independent of each other, although the surface area of the P wave and the cardiac rate present an interrelationship. It was further demonstrated that the cardiac rate irrespective of the surface area of the P wave influences the appearance and the degree of displacement of the P-T_a segment. On the other hand, it was apparent that the height of the P wave increased with the cardiac rate and because of this also increased the surface area of the P wave. Consequently, the cardiac rate exerts a double influence upon the P-T_a segment—direct and indirect—the latter through the surface area of the P wave.

Because the cardiac rate and the surface area of the P wave combine in determining the incidence and displacement of the P-T_a segment, their concerted action was examined by means of the minute surface area that unites both factors in a single expression by multiplication. The minute surface areas classed according to their numerical values presented some typical features regarding the P-T_a segment. Below a minute surface area of 100 m.v.s., no P-T_a segment was visible. The minute surface area of 400 m.v.s., called the lower threshold level, separates records below that critical value, with a rare appearance of a visible P-T_a segment, about 23 per cent, from those cases above 400 m.v.s. where the P-T_a segment is visible rather frequently, e.g., from 401 to 500 in 64 per cent. The upper threshold level, 800 m.v.s., can be defined

by asserting that above it a visible P-T_a segment occurs in 100 per cent of the cases. As to the degree of the displacement of the P-T_a segment greater displacement is usually found at higher numerical values of the minute surface area, but this parallellism cannot be expressed in a mathematical equation.

Finally, it can be stated that the displacement of the P-T_a segment is determined by two factors: the cardiac rate and the surface area of the P wave. These empirically found facts agree closely with recent electrocardiographic interpretations. Scherf and Schaffer,[25] discussing the causes of the deepening of the T_a wave after effort, state that this change is only partly due to the increased size of the P wave; the main reason is, however, the tachycardia that follows exercise. According to the current theory of the T_a wave, the area subtended by the P wave is equal in size and opposite in direction to the area of the T_a wave. Furthermore, the same authors maintain that the duration of the monophasic action current of the myocardial elements decreases as the heart rate increases. The shortening of the monophasic action current chiefly involves the recovery phase, which inscribes the T_a wave. As the T_a wave shortens, it must deepen in order to maintain an area equal and opposite to that of the P wave. This interpretation of electrocardiographic events during tachycardia satisfies both theory and experience. In the present study only changes of the P-T_a segment were measured because the auricular T_a wave itself is invisible in normal conditions. However, increased deepening of the P-T_a segment with increasing cardiac rate, as was quantitatively established, represents the same electrophysiologic principle of maintenance of the equality of surface area between P and T_a waves by increasing depth with shortened duration.

Experiences obtained in the clinical field confirm these established basic correlations. In a reduced number of cases, specially selected records as demonstrative for each condition were studied. Average cardiac rate of the mitral valvular patients was 92 and that of the pulmonary patients 89 per minute; both frequencies belong to that zone where incidence of the P-T_a segment is 100 per cent. Intensity of the displacement of the P-T_a segment in the two groups was markedly increased. This increase is exclusively due to the increased size of the P wave. The average displacement of the P-T_a segment corresponding to each cardiac rate, as found in the measurements made in healthy individuals, reached 0.5 mm., whereas, in the group of patients with mitral valvular disease the average measured displacement was 0.89 mm., i.e., about 80 per cent more than corresponded to the factor of cardiac rate. Surface area averaged at a cardiac rate of 90 per minute in healthy individuals, 6.0 m.v.s.; whereas, in patients with mitral valvular disease the average surface area measured 13.15 m.v.s., thus presenting a difference of 120 per cent. The same comparison realized in the group of pulmonary patients indicated that the average displacement of the P-T_a segment was 0.74 mm., i.e., about 50 per cent greater than corresponded to the average cardiac rate; whereas, the average surface area of the P wave with its numerical value of 9.2 m.v.s. was 53 per cent greater than in normal cases.

The decisive influence of the cardiac rate on the displacement of the P-T_a segment is still not sufficiently appreciated. In a recent paper, Jaruszewsky and associates[26] report electrocardiographic observations made during cardiac surgery. They divided patients into different groups, but the changes registered were identical in each case. The most striking electrocardiographic change consisted in a very pronounced depression of the T_a wave and S-T segment, observed in all cases. According to these authors the changes are conditioned by altered dynamics of the right side of the heart, by strain of the right auricle and ventricle, and concomitant hypoxia. However, the authors observed a very rapid heart rate in each group. For example, in the group of patients with patent ductus arteriosus (45 cases) the average cardiac rate before anesthesia was 92, and after induction of the anesthesia it increased to 129; a further increase to 139 was observed when the pleura was opened. During dissection of the ductus the average heart rate increased to 148 beats per minute and remained in this range until suture of the chest wall. There is no doubt that in these cases the principal cause of the marked displacement of the P-T_a segment is the intense tachycardia apart from altered cardiodynamics and/or anesthesia. As found in the present study, displacement of the P-T_a segment occurred in 100 per cent of the cases when cardiac rate surpassed 90 beats per minute. With the cardiac rates of 130 to 150 observed by the authors, no single case could fail to display a very marked displacement of the P-T_a segment. This conclusion is further supported by the results of the exercise test, when in healthy adults a tachycardia of 120 to 130 beats per minute is sometimes present. In these cases the P-T_a segment may exhibit a displacement as deep as 2 mm. or even more, and this disappears after a short period of rest. The electrocardiographic changes with reference to the P-T_a segment during cardiac surgery and in the exercise test are identical in spite of entirely different cardiodynamic mechanism, yet there exists a common factor in both cases: the tachycardia, which explains the modifications of the T_a wave.

SUMMARY

1. Displacement of the P-R interval, the only visible section of the auricular T wave in the normal electrocardiogram, has been studied with special reference to the cardiac rate.

2. Displacement of the P-T_a segment is determined by two factors which are the cardiac rate and the surface area of the P wave. Both factors present a direct correlation with the incidence and the intensity of the displacement of the P-T_a segment, both separately and combined, when it is expressed by the minute surface area.

3. The P-T_a segment is practically invisible at cardiac rates below 70 beats per minute, it becomes increasingly visible from 71 to 90, and over a cardiac rate of 91 it is constantly present.

4. The average displacement of the P-T_a segment increases with increasing cardiac rates.

5. The height and the surface area of the P wave present a direct correlation both with the incidence and the degree of displacement of the P-T_a segment, independently of the cardiac rate.

6. The numerical value of the minute surface area, with regard to the P-T_a segment, presents two threshold levels. Below the lower threshold level of 400 m.v.s., the P-T_a segment is visible only occasionally; over the upper threshold level of 800 m.v.s. a visible P-T_a segment is constantly present. In the middle zone from 400 to 800 m.v.s., the P-T_a segment becomes increasingly visible.

7. Displacement of the P-T_a segment is a physiologic phenomenon and is found constantly in the normal electrocardiogram under established conditions and is therefore devoid of clinical and pathologic significance.

8. The established quantitative correlations have also been proved to be valid in the clinical field as it was demonstrated in the groups of patients studied with mitral valvular lesion and with chronic cor pulmonale.

9. Certain pathophysiologic considerations are made concerning the mechanism and significance of the described correlations.

SUMMARIO IN INTERLINGUA

1. Duo factores determina le displaciamento del intervallo P-R (que es le sol segmento visibile del unda auricular T in normal electrocardiogrammas). Iste factores es le frequentia cardiac e le area del unda P.

2. A frequentias cardiac infra 70, le segmento P-T_a es practicamente invisibile. Illo deveni progressivemente plus visibile con frequentias cardiac ab 71 a 90, e con frequentias cardiac supra 91 illo es semper presente.

3. Le altitude e le area del unda P se trova in correlation directe con tanto le frequentia como etiam le grado del displaciamento del segmento P-T_a.

4. Le displaciamento del segmento P-T_a es un phenomeno physiologic. Sub certe conditiones illo se incontra constantemente in le electrocardiogramma normal. Ergo su presentia non signala necessarimente un situation pathologic.

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BILATERAL BUNDLE BRANCH BLOCK

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IN MOST cases of complete atrioventricular (A-V) block it is assumed that the organic lesions or functional disturbances responsible for the interruption of the A-V conduction are located in the Aschoff-Tawara node or in the bundle of His. However, careful anatomic studies have shown that in about 20 per cent of the clinical cases of complete A-V block, interruption in the continuity of both branches of the bundle of His could be considered responsible.[73] This is in full accordance with the classical theory of the function of the A-V conduction system and with the great frequency with which bundle branch block of either the right or left bundle are observed in human clinical cases. It is then rather surprising that the diagnosis of complete A-V block due to bilateral bundle branch block should not be more frequent. In fact, we can safely state that almost no electrocardiographer ever signs such a report in cases of complete A-V block. The reason for this is that the electrocardiographic pattern is similar or identical in complete A-V block, no matter whether the anatomic lesion is located in the principal stem (including the A-V node) or in the branches of the conducting system. It is true that when in the former case the QRS complex has a supraventricular form, bilateral bundle branch block can practically be excluded. But, as in 30 to 80 per cent of the cases of complete A-V block, the QRS complex is of the idioventricular type,[14,60,63,73] the problem is still present in most of the instances.

Wilson and Herrmann,[69,70] in complete A-V block produced by section of both branches of the bundle of His, observed changes in the configuration of the idioventricular beats which they attributed to displacements of the ventricular pacemaker from one to the other ventricle and suggested that a diagnosis of bilateral bundle branch block becomes probable when similar changes are observed in clinical cases of complete A-V block. Even though on some occasions this sign is utilized to make the diagnosis of bilateral bundle branch block, its reliability has been questioned by the reported cases in which changes of the idioventricular beats were observed in the presence of lesions of the bundle of His.[20]

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Presented in part Sept. 13, 1954, at the Second World Congress of Cardiology, Washington, D. C.

This investigation was aided by the Grant H-1486 of the National Heart Institute, National Institutes of Health, United States Public Health Service.

Received for publication Nov. 24, 1954.

*This work was done during the tenure of an Established Investigatorship of the American Heart Association.

A definite diagnosis of bilateral bundle branch block can be made in some exceptional cases in which conduction in both branches is only partially interrupted and in which changes in the comparative degree of block in the two branches allow the patterns of right and left bundle branch block to appear alternately or intermittently in the same patient. In this paper, two cases of this sort will be reported and a review and discussion of similar previously reported cases will be attempted.

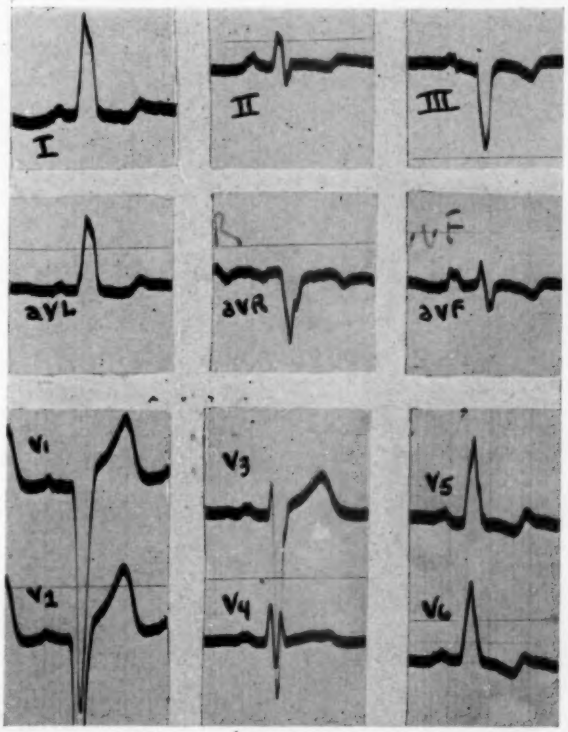


Fig. 1.—Case 1. ECG 1. Left bundle branch block pattern. See text.

CASE REPORTS

CASE 1.—C.M., a 56-year-old woman. Her principal complaints were palpitations, noncharacteristic precordial pain, and dyspnea of the nervous type. Physical examination revealed a rather obese woman with a soft and nonpropagated systolic murmur in the aortic area. The blood pressure (on many different occasions) oscillated between 190/110 and 270/130 mm. Hg, no signs of heart failure were ever present. Recently the patient experienced on two occasions a very short-lasting sensation of fainting, without syncope. The radiologic examination showed a ++ enlarged left ventricle.

Thirty electrocardiograms were recorded from April, 1951, to September, 1953. A short description of each of them will be helpful for a better understanding of the time sequence of the different abnormalities observed.

1. April 10, 1951. Left bundle branch block. P-R, 0.16 sec. QRS, 0.11 to 0.12 sec. P-P intervals, 0.63 to 0.73 sec. $\hat{A}_{QRS}$, −15° (Fig. 1).

2. April 14, 1951. Different degrees of left bundle branch block. P-R, 0.15 sec. QRS, 0.08 to 0.12 sec. P-P intervals, 0.66 to 0.74 sec. Negative T waves in Leads aV_F, II, and III.

3. April 19, 1951. Incomplete left bundle branch block. P-R, 0.16 sec. QRS, 0.07 sec. P-P intervals, 0.65 to 0.75 sec. Negative T waves in Leads aV_F, II, III, and right precordial leads. Elevated S-T segment in the same leads.

4. April 25, 1951. Most of the beats show apparently normal intraventricular conduction and some of them the pattern of left bundle branch block. The same abnormalities of the S-T segment and T wave as in ECG 3. P-R, 0.15 sec. QRS, 0.06 to 0.12 sec. P-P intervals, 0.63 to 0.68 sec. (Fig. 2).

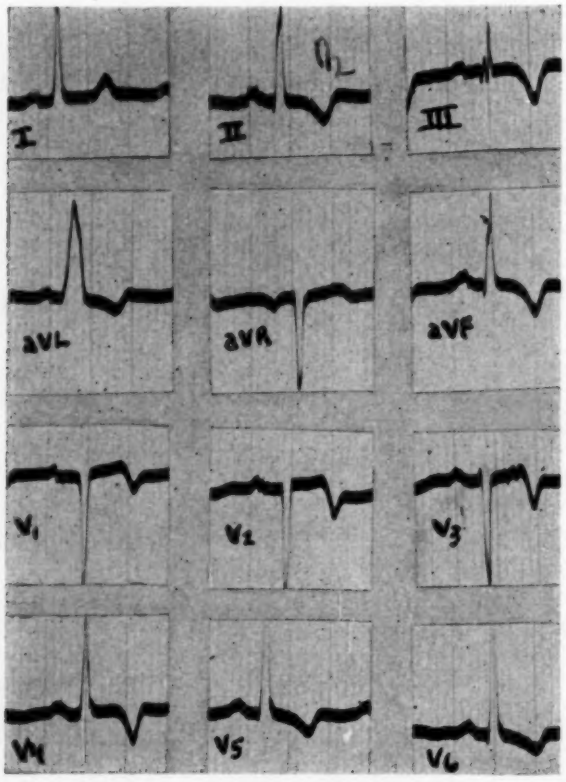


Fig. 2.—Case 1, ECG 4. Almost normal intraventricular conduction. See text.

5. May 12, 1951. Most of the beats apparently show normal intraventricular conduction, some of them, incomplete left bundle branch block. The T waves became positive in all the precordial leads and less negative in Leads aV_F, II, and III. P-R, 0.15 sec. QRS, 0.08 to 0.10 sec. P-P intervals, 0.75 to 0.91 sec.

6. May 22, 1951. Right bundle branch block. P-R, 0.20 sec. QRS, 0.12 sec. P-P intervals, 0.70 sec. $\hat{A}_{QRS}$, + 30°. The S-T segment and T-wave abnormalities described in the previous tracings are no longer present (Fig. 3).

7. May 23, 1951. Left bundle branch block. Occasional beats show normal intraventricular conduction. P-R, 0.16 sec. QRS, 0.08 to 0.12 sec. P-P intervals, 0.73 to 0.87 sec. (Fig. 4,*A*).

8. May 26, 1951. As in ECG 7, but a greater number of beats show normal intraventricular conduction. P-P intervals, 0.81 to 0.93 sec.

9. June 1, 1951. Left bundle branch block. P-R, 0.16 sec. QRS 0.13 to 0.14 sec. P-P intervals, 0.66 to 0.78 sec. (Fig. 4,*B*).

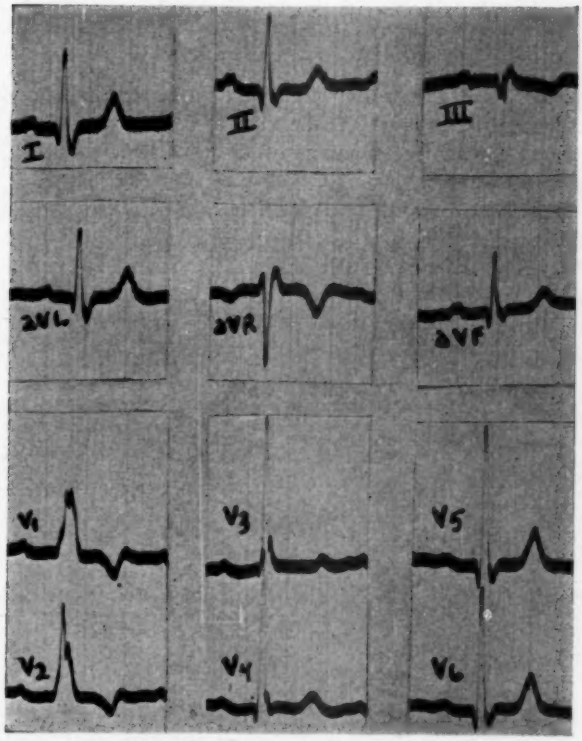
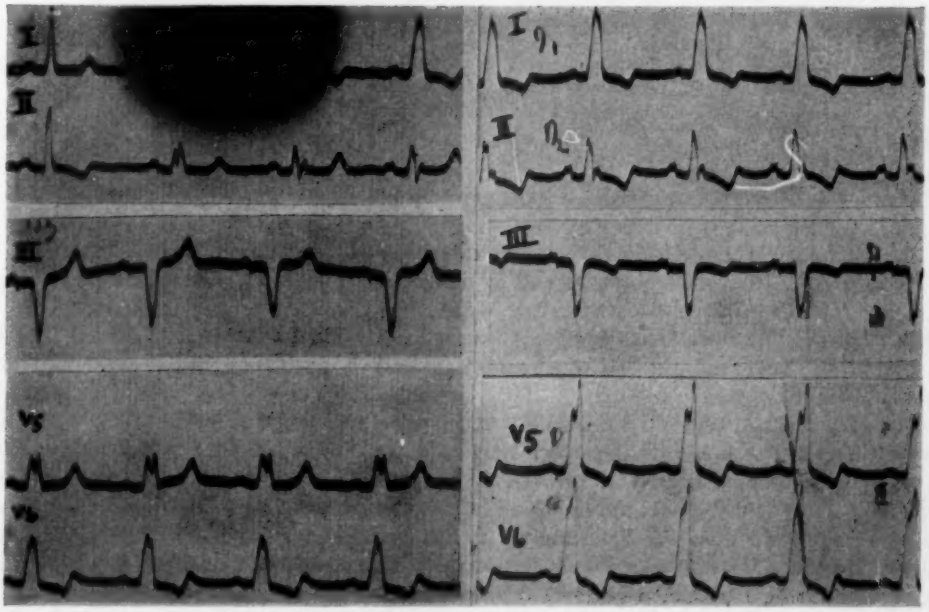


Fig. 3.—Case 1, ECG 6. Right bundle branch block pattern. See text.



A. *B.*

Fig. 4.—*A* and *B*. Case 1, ECG's 7 and 9. Different degrees of left bundle branch block. See text.

10. June 5, 1951. Left bundle branch block. P-R, 0.16 sec. QRS, 0.12 sec. P-P intervals, 0.71 to 0.82 sec.

11. June 9, 1951. Left bundle branch block. P-R, 0.16 sec. QRS, 0.11 sec. After the injection of 1 mg. of Atropine sulfate intramuscularly and after the performance of a mild exercise, almost the same results were observed: the heart rate rose from 80 to 135 beats per minute; the P-R interval remained the same. Massage of the carotid sinus had no effect on the heart rate. The QRS complex did not change.

12. June 15, 1951. Left bundle branch block. P-R, 0.16 sec. QRS, 0.12 sec. P-P intervals, 0.76 to 0.80 sec.

13. July 18, 1951. As in ECG 12. P-P intervals, 0.64 to 0.70 sec.

14. Aug. 29, 1951. As in ECG 12. P-P intervals, 0.65 to 0.76 sec.

15. Oct. 23, 1951. Different degrees of left bundle branch block. P-R, 0.15 sec. QRS, 0.08 to 0.12 sec. P-P intervals, 0.68 to 1.00 sec.

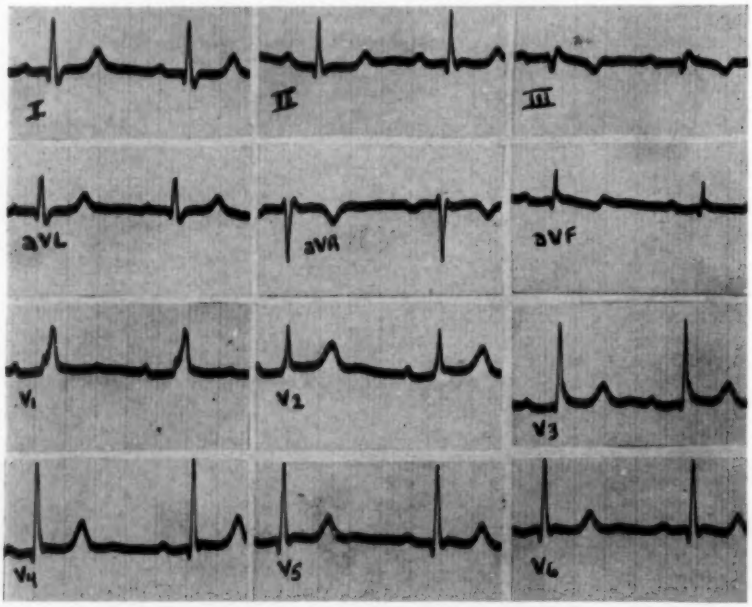


Fig. 5.—Case 1, ECG 18. Permanent right bundle branch block. See text.

16. Oct. 31, 1951. As in ECG 12. P-P intervals, 0.67 to 0.73 sec.

17. Dec. 14, 1951. Different degrees of incomplete left bundle branch block. P-R, 0.16 sec. QRS, 0.08 to 0.12 sec. P-P intervals, 0.75 to 0.95 sec.

18. March 20, 1952. Right bundle branch block. P-R, 0.22 sec. QRS, 0.12 sec. P-P intervals, 0.79 to 0.90 sec. On only one occasion, after a dropped beat, the P-R interval became 0.20 sec. (Fig. 5).

19. March 22, 1952. Right bundle branch block. P-R, 0.12 sec. QRS, 0.12 sec. A very long tracing was taken during which numerous transitions from 1:1 to 2:1 conduction and vice versa were observed (Fig. 6, *A* and *B*). In the presence of 2:1 A-V block, the P-R interval was about 0.19 to 0.20 sec. and the sinus rate was always over 90 beats per minute. During the periods of 1:1 conduction, the P-R interval varied between 0.20 and 0.26 sec. (Wenckebach periods), and the sinus rate was always less than 80 beats per minute. The following changes were observed after the patient performed moderate exercise; immediately after the end of the test, complete A-V dissociation occurred with sinus and ventricular rates of 166 and 49 per minute, respectively (Fig. 6,*C*). During the progressive slowing of the sinus rate, conducted beats began to appear, partly as fusion beats, with a P-R interval oscillating between 0.20 and 0.32 sec. At the end of the first minute this was transformed into 3:1 A-V block during which the conducted

beats showed a P-R interval of 0.28 sec. (Fig. 6,*D*). At the end of the second minute 2:1 and 1:1 conduction reappeared. At this moment, bigeminal ectopic ventricular beats occurred, which gave place again to 3:1 A-V block. One minute later the ectopic beats disappeared and 2:1 A-V block persisted for a long time.

20. March 24, 1952. Right bundle branch block. P-R, 0.20 sec. QRS, 0.12 sec. P-P intervals, 0.83 to 1.05 sec.

21. March 29, 1952. As in ECG 20, with occasional dropped beats.

22. May 3, 1952. As in ECG 20, with periods of 2:1 A-V block. P-P intervals, 0.61 to 0.82 sec.

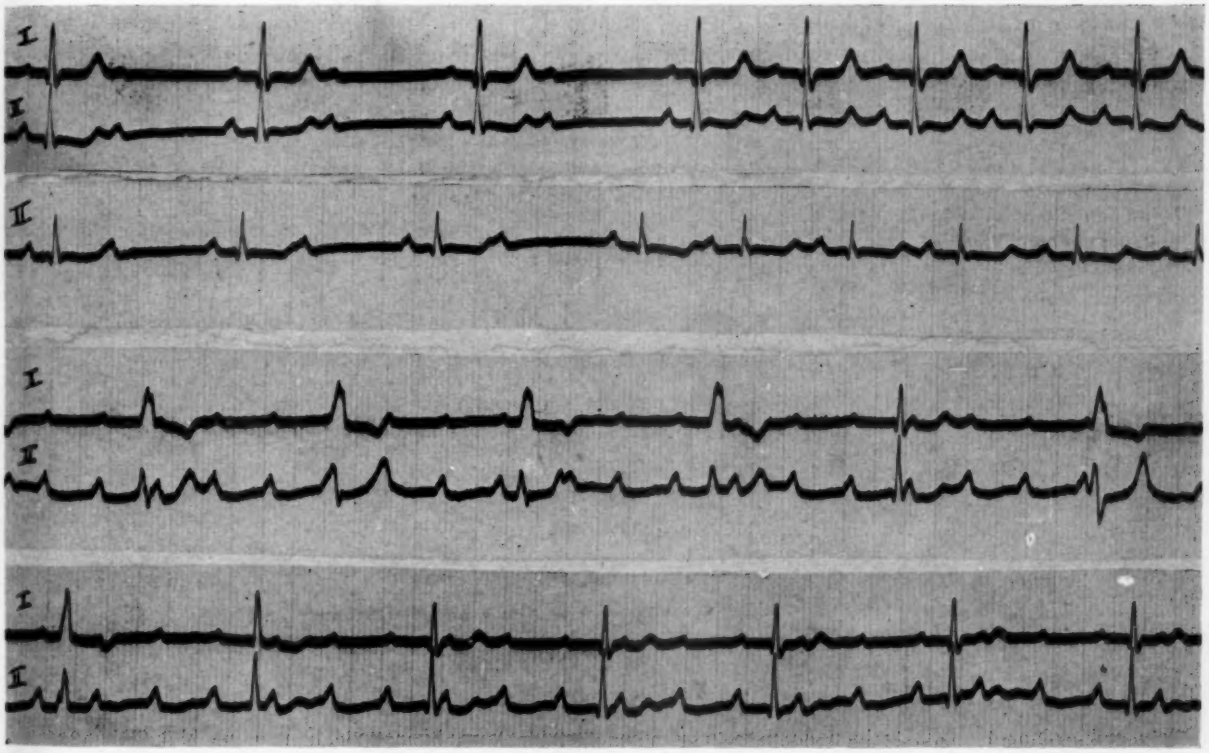


Fig. 6.—Case 1, ECG 19. *A* **and** *B*, **Transitions between 2:1 and 1:1 conduction.** *C* **and** *D*, **Effect of exercise. See text.**

23. July 10, 1952. Transitions from 1:1 to 2:1 conduction, Wenckebach periods, occasional dropped beats.

24. Aug. 23, 1952. As in ECG 23.

25. Nov. 13, 1952. As in ECG 23.

26. Jan. 20, 1953. As in ECG 23.

27. March 7, 1953. Right bundle branch block. P-R, 0.22 sec. QRS, 0.12 sec. P-P intervals, 0.70 to 0.77 sec. 1:1 conduction with occasional dropped beats. After a mild exercise, the sinus rate rose from 80 to 130 and 2:1 A-V block occurred.

28. May 6, 1953. Right bundle branch block. P-R, 0.21 sec. QRS, 0.12 sec. P-P intervals, 0.80 to 0.85 sec. 1:1 conduction.

29. Aug. 21, 1953. P-P intervals, 0.61 to 0.70 sec. 2:1 A-V block. Occasional ventricular escapes (Fig. 7,*A*).

30. Sept. 2, 1953. As in ECG 29 (Fig. 7,*B*).

The first five electrocardiograms showed in different beats normal intraventricular conduction or different degrees of left bundle branch block. The QRS duration varied between 0.06 and 0.12 sec., and the P-R interval was in every case 0.15 to 0.16 sec. The changes of the S-T segment and T waves at this time were compatible with acute myocardial infarction possibly involving the anterior and posterior walls of the left ventricle in the vicinity of the interventricular septum, which was also probably affected. This conclusion was supported by the presence of QS complexes in Leads V_1 and V_2. However, it must be mentioned that the patient did not present clinical symptoms of myocardial infarction preceding or during the period when these electrocardiograms were obtained and that the sedimentation rate remained normal throughout the same interval.

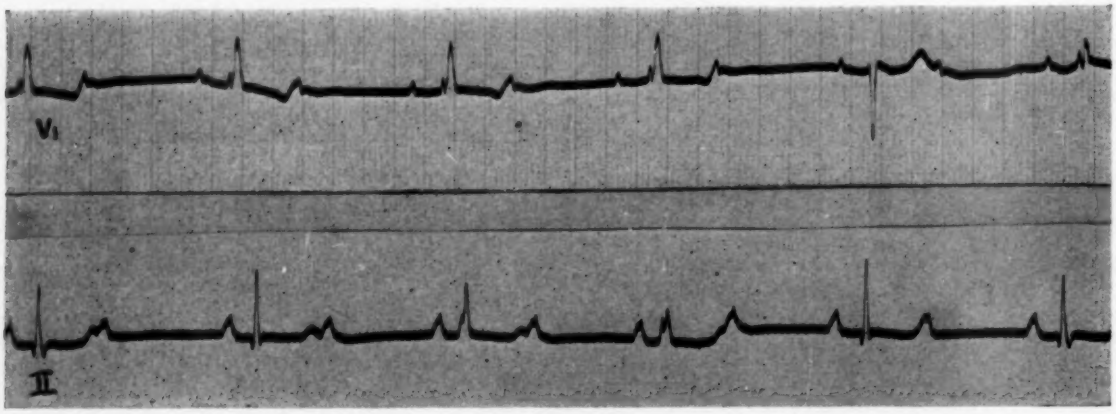


Fig. 7.—Case 1, ECG 30. 2:1 A-V block with occasional ventricular escapes. See text.

The sixth electrocardiogram (taken ten days after the fifth) showed right bundle branch block, and then, for the first time, the P-R interval was prolonged to 0.20 sec. On the next day, the seventh electrocardiogram again showed varying degrees of left bundle branch block, with the P-R interval returning to the normal value of 0.16 sec. The following ten tracings were similar to the first five and to the seventh, showing normal intraventricular conduction or varying degrees of left bundle branch block and the P-R interval never exceeded 0.15 to 0.16 sec. When right bundle branch block reappeared in the eighteenth electrocardiogram, the P-R interval was again prolonged to 0.22 sec., and for the first time, a dropped beat was observed. From then on, in the next twelve tracings, right bundle branch block became permanently established and different forms of A-V block developed (isolated dropped beats, 2:1 A-V block, Wenckebach periods); normal A-V conduction was never regained. After an exercise test even transitory complete A-V dissociation was produced.

The electrocardiograms 1 to 5 and 7 to 17 are definite evidence that during the eight months during which they were registered the patient had a conduction disturbance in the left branch of the bundle of His. Although in some of these

tracings the width of the QRS was 0.12 sec., it is clear that conduction at this time was not completely interrupted in the left branch, for in the electrocardiogram 9 the width of QRS was 0.13 to 0.14 sec. probably corresponding to complete left bundle branch block. The fact that in all the tracings showing left bundle branch block the P-R interval never exceeded 0.15 to 0.16 sec. proves that in these instances conduction in the right branch of the bundle of His was normal. Otherwise, some degree of A-V block should have been observed, which was never the case.

The electrocardiograms 6 and 18 to 30 showed a typical pattern of right bundle branch block, with a QRS of 0.12 sec. The fact that whenever right bundle branch block was present the width of QRS was always 0.12 sec. and the form of the ventricular complex was invariably the same suggests that in this case the interruption of conduction in the right branch was "complete" from a functional point of view. The case of electrocardiogram 6, when right bundle branch block appeared for a period of time which could not have exceeded ten days, suggests that, at this time, the interruption was not complete from an anatomic point of view. Whether or not the right bundle was anatomically interrupted during the time when electrocardiograms 17 to 26 were taken, we can not definitely say.

In contrast with the pattern of left bundle branch block always being accompanied by normal A-V conduction, the pattern of right bundle branch block was always accompanied by definite evidences of impaired A-V conduction. When the right bundle branch block became established in permanent form (electrocardiograms 18 to 30), every type and degree of A-V block was observed (prolonged P-R intervals, occasional dropped beats, Wenckebach periods, 2:1 and 3:1 A-V block and transient complete A-V dissociation immediately after exercise). When right bundle branch block was a transient phenomenon interrupting the series of tracings with left bundle branch block, it was accompanied by a prolonged P-R interval of 0.20 sec. (electrocardiogram 6). The next day, when right bundle branch block disappeared the P-R interval returned to its normal value of 0.16 sec.

The impairment of A-V conduction, which was always associated with the right bundle branch block pattern, must undoubtedly be related to the "partial" or "incomplete" left bundle branch block that was present on both occasions prior to the appearance of the former and represents the degree of delay of the stimulus in traversing the left branch and not the A-V node or the main stem of the bundle of His. This means that when right bundle branch block appeared, the "incomplete" left bundle branch block did not disappear but became manifest as an impairment of the A-V conduction. The possibility that the appearance of right bundle branch block was accompanied by a true A-V conduction disturbance located in the A-V node or in the bundle of His, with a simultaneous disappearance of the left bundle branch block, is so remote that it does not require further discussion, especially as the same situation was observed twice in the series of electrocardiograms. The sequence of the fundamental events

of the case is schematically represented in Fig. 8. The normal P-R interval or time of A-V conduction includes the auricular conduction time (from the sinus node to the A-V node), the delay in the A-V node, and the time of conduction in the bundle of His and its branches, till the excitation wave arrives to the first ventricular muscle to be activated. It is very well known that most of this interval is due to the delay of the stimulus in the A-V node, where conduction velocity is the lowest of all the different parts of the heart muscle. The conduction time in the bundle of His and in both branches, on the contrary, is usually disregarded, being considered as an insignificant part of the total P-R interval. It is also a well known fact that the excitation wave arrives first at the left side of the septum. This difference does not exceed 0.02 sec. In Fig. 8,*A* the total conduction time from the sinus node to the right ventricle is assumed to equal 0.16 sec. while that to the left ventricle equals 0.14 sec. The shorter of these conduction times represents the actual P-R interval. Both P-R intervals have a common part, which is normally the greatest component of the A-V conduction time. If conduction is impaired in the "common part" of the P-R interval, different forms of A-V block may occur, but the right and left P-R interval will be equally prolonged.

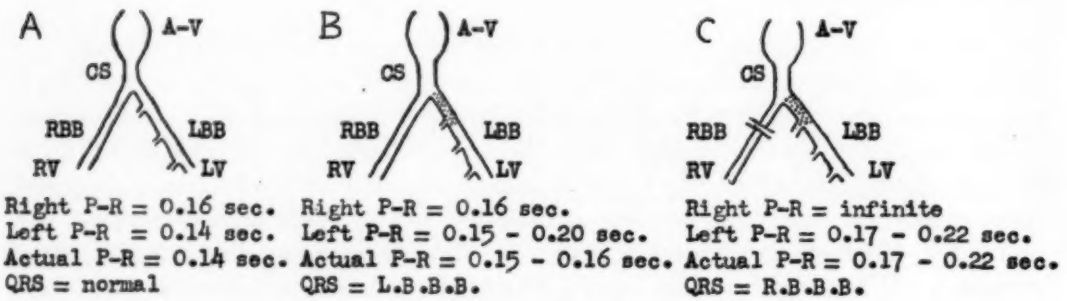


Fig. 8.—Schematic representation of the influence of bundle branch block on the P-R interval (see text). *A*, Normal conduction. *B*, Incomplete left bundle branch block. *C*, Incomplete left with complete right bundle branch block. A-V = atrioventricular node. CS = common stem of the Bundle of His. RBB and LBB = right and left bundle branches. RV and LV = Nonspecific right and left ventricular muscle.

In Fig. 8,*B*, a delay of 0.01 to 0.06 sec. has been assumed to be present in the left branch, while conduction remained unchanged in the rest of the conduction system. It is clear that the right P-R interval will be 0.16 sec. as before and that the left P-R interval will be now 0.01 to 0.06 sec. longer, that is, 0.15 to 0.20 sec. It is also clear that in the corresponding electrocardiogram, the actual P-R interval will be equal to the right P-R interval (that is to the shorter of both intervals) and consequently will not be prolonged by more than 0.02 sec. The QRS complex will show different degrees of left bundle branch block: the smallest possible when the delay is around 0.01 sec., the greatest when the delay is 0.04 to 0.06 sec. As this latter interval is the maximal assumed time necessary for the stimulus to traverse the septum and so to activate the contralateral ventricle before the excitation wave arrives via the affected branch, further prolongation of the conduction time in this branch cannot increase the degree

of bundle branch block as seen in the electrocardiogram. The situation illustrated in Fig. 8,*B* applies to all the electrocardiograms of Case 1 in which left bundle branch block was present (ECG 1 to 5 and 7 to 17).

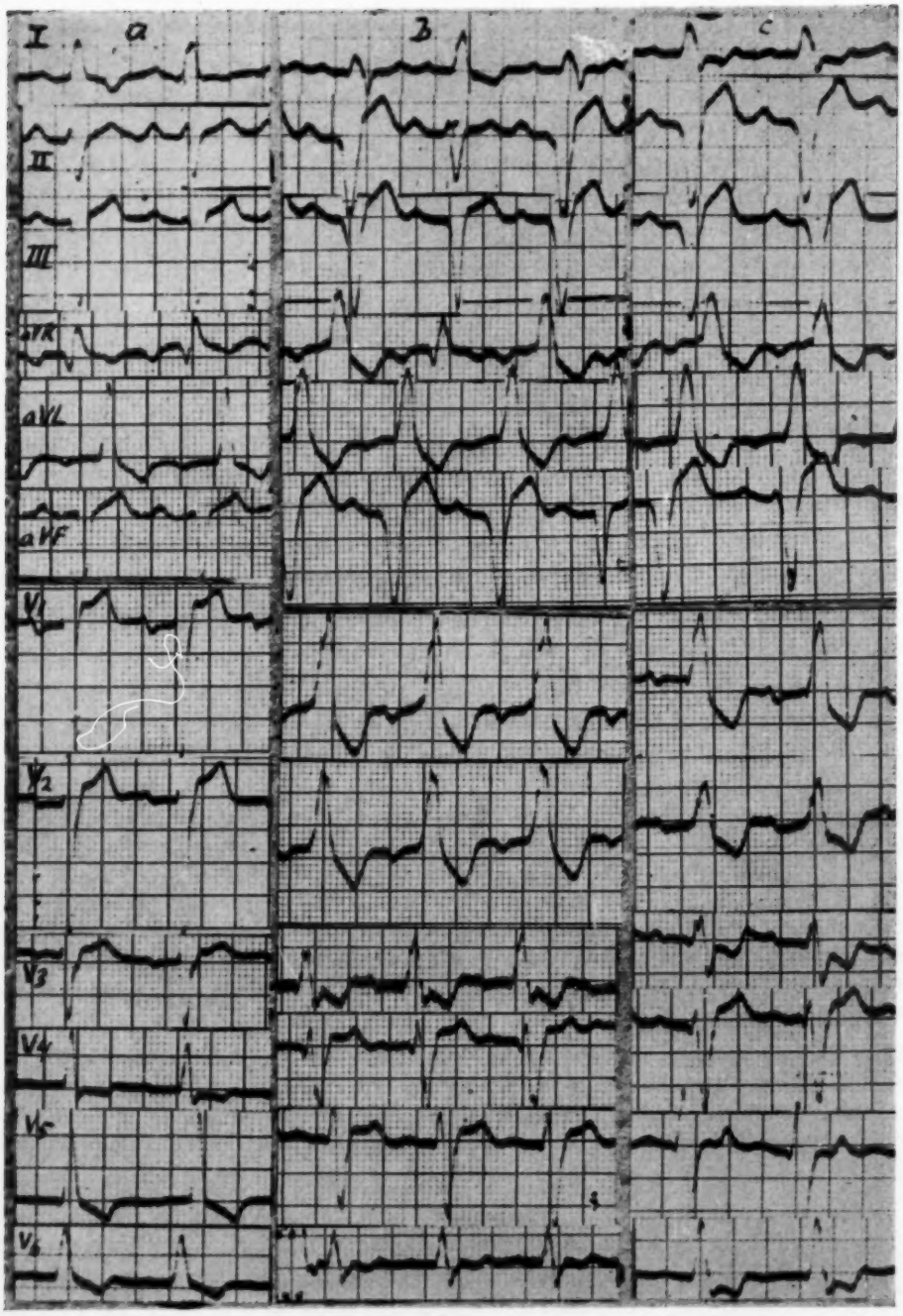
In Fig. 8,*C*, complete interruption of conduction in the right bundle branch was added to the situation of Fig. 8,*B*. In this condition, the stimulus must inevitably reach the ventricles through the left branch, the electrocardiogram will show the pattern of right bundle branch block, and the actual P-R interval will depend on the conduction delay existing in the left branch. The difference between the P-R interval before and after the appearance of right bundle branch block represents the measurable conduction delay in the left branch of the bundle of His. The situation illustrated in Fig. 8,*C* applies to all the electrocardiograms of Case 1 in which right bundle branch block was present (ECG 6, and 18 to 30). Thus from electrocardiogram 6, where P-R was 0.20 sec., we can deduce that the conduction delay in the left branch was 0.06 sec. for that particular tracing. In a similar way, electrocardiogram 18, where P-R was 0.22 sec., indicated a delay of 0.08 sec. and occasional sudden complete interruption of conduction (dropped beats). Electrocardiogram 19 demonstrated in the left branch all the typical forms of conduction block as they are usually seen in the different types of A-V block attributed to organic or functional alterations located in the A-V node or in the main stem of the bundle of His. The same considerations can be applied to tracings 20 to 30.

CASE 2.—T.F., a 59-year-old man with arteriosclerotic heart disease, normal blood pressure, and signs of heart failure had considerable enlargement of the left ventricle at fluoroscopic examination. He had frequent loss of consciousness of the Adams-Stokes syndrome type and died during one of these episodes. No autopsy was performed.

The electrocardiogram taken during his first admission to the hospital (Fig. 9,*A*) showed left bundle branch block, with a QRS of 0.14 sec. and a P-R interval of 0.24 sec. A second electrocardiogram taken four months later, immediately following one of the episodes of loss of consciousness (Fig. 9,*B*), showed periods of alternation of right and left bundle branch block (in Leads I, II, III, and aV_R). The third tracing, taken one hour after the second one, showed right bundle branch block only. The QRS complex measured 0.16 sec. and the P-R interval 0.21 sec. (Fig. 9,*C*). The direction of the mean electrical axis of QRS was $-60°$ with the left and $-75°$ with the right bundle branch block patterns.

There are minor differences between the right bundle branch block patterns in Fig. 9,*B* and *C*. In Leads I and V_6 of the latter, the R waves are taller and the T waves predominantly inverted. This difference could be accounted for by a more horizontal position of the heart. The inverted T waves in left ventricular leads in this case were probably due to left ventricular hypertrophy.

In this case, both right and left bundle branch block were accompanied by a prolonged P-R interval, which was about 0.03 sec. longer for the left type of ventricular complexes. For the electrocardiogram of Fig. 9,*A*, we can assume that the "right P-R interval" was about 0.24 sec. and the "left P-R interval" was longer than that, without complete interruption of conduction in the left branch. Thus the electrocardiogram showed a typical pattern of left bundle branch block and the prolonged P-R interval was due to the delay of conduction in the right branch and not in the main stem of the His bundle or in the A-V node.



A. *B.* *C.*

Fig. 9.—Case 2. *A*, **Left bundle branch block.** *B*, **Alternating right and left bundle branch block patterns.** *C*, **Right bundle branch block. See text.**

In the electrocardiogram of Fig. 9,*C*, the left P-R interval was about 0.21 sec. and the right P-R interval was now longer, so that a pattern of right bundle branch block was present and the prolonged P-R interval was due to the delay in the left branch of the His bundle. The alternation of right and left bundle branch block in Fig. 9,*B* can be explained by the assumption of 2:1 right bundle branch block in the presence of a permanent incomplete left bundle branch block or 2:1 right or left bundle branch blocks alternating with each other. This alternation, registered immediately after the Adams-Stokes attack, indicates a greater impairment of conduction than was present at other times and justifies the assumption that this attack was caused by complete bilateral bundle branch block.

DISCUSSION

The prevalent belief that interruption of conduction in both branches of the bundle of His causes complete A-V block is supported by many experimental observations.[7,17,70*] But more important in relation to the subject of this paper are the experiments in which only one branch was completely interrupted, while partial or incomplete block was simultaneously produced in the opposite branch. In these conditions, the excitation wave must reach the ventricles through the partially blocked branch, and as the A-V node and bundle of His are supposed to be unaffected in the course of the experiment, any disturbances of the A-V conduction will be a measure of the impairment of conduction in the partially blocked branch. Scherf and Shookhoff,[46] by sectioning one of the branches and temporarily compressing the other one between its middle and upper third, could observe different degrees and forms of A-V block, (prolonged P-R intervals, Wenckebach periods, 2:1, 3:2, and 4:3 A-V block, etc.). Similar experimental observations have also been reported by Wilson and Herrmann.[70]

The close resemblance of Case 1 to the experimental observations of Scherf and Shookhoff is evident. In this case, all the forms of impaired conduction in one of the branches of the bundle of His could be objectively demonstrated, since they appeared as changes of the A-V conduction. Similar changes of the A-V conduction were present in other published cases in which during sinus rhythm both right and left bundle branch block were alternately or intermittently present in the same patient.

Stenström[59] in 1927 reported a case (No. 3) in which ventricular complexes of the right bundle branch block pattern of constant shape and width uninterruptedly alternated with ventricular complexes of the left bundle branch block type, but of almost continuously changing width (various degrees of left bundle branch block). Although no precordial leads were taken and the corresponding curves are labeled according to the old nomenclature, the standard leads allow us to recognize typical patterns of right and left bundle branch block. While the left bundle branch block complexes were always preceded by a P-R interval of about 0.16 sec., the right bundle branch block complexes were always accompanied by some degree of A-V block, the P-R intervals ranging from about 0.22 to 0.25 sec. The following explanation suggested by Stenström

*The observations according to which section (Robb and associates)[39] or degeneration (Field [18] of the main stem or both bundle branches did not produce complete A-V block were attributed to the presence of early branches originating from the common stem.[28,32-34,39] However, these connections were found only in a small percentage of cases; they may play a role in the atypical cases of bilateral bundle branch block mentioned at the end of this paper.

seems to be most plausible: "partial block of the 2:1 type in the right branch and simple prolongation of conduction time without dropped beats in the left branch were assumed to be present. In the beats in which conduction was completely blocked in the right branch (right bundle branch block type of ventricular complexes), the excitation wave arrived at the ventricles with the delay determined by the permanent conduction disturbance in the left branch, and so the P-R interval was always prolonged in these instances (0.22 sec. to 0.25 sec.). In the beats in which the stimulus traversed the right branch, it did so without any delay, in the same way as in simple 2:1 A-V block the P-R interval of the conducted auricular beats may be normal. Consequently, these beats had a normal P-R interval (around 0.16 sec.) and the ventricular complexes were of the left bundle branch block type, for the left branch was assumed to have a permanent prolongation of its conduction time. The fact that different degrees of left bundle branch block were observed is in accord with the variation in the P-R intervals of the right bundle branch block complexes and may be related to different degrees of recovery of the left branch after the alternate beats in which the whole heart was probably activated through the right branch, or to small spontaneous changes in its conductivity."

In 1940, Mortensen[37] published a case in which right and left bundle branch block seemed to be present in the same patient, sometimes alternating in the same electrocardiogram. The P-R interval was normal in the right and prolonged in the left bundle branch block complexes. The direction of $\hat{A}_{QRS}$ was about $-120°$ in the former and about $+60°$ in the latter. In this case the only reproduced precordial lead (CF_2) seemed to support the true existence of right and left bundle branch block, and the electrocardiogram can then be interpreted as showing 2:1 left bundle branch block, in the presence of prolonged conduction in the right bundle branch, or of alternating 2:1 left and right bundle branch block.

A case reported by Dressler[16] (Case 2) seemed to be a typical instance of alternating right and left bundle branch block, as confirmed by the precordial leads. The P-R interval was 0.21 sec. for the right and 0.16 sec. for the left type of ventricular complexes. Dropped beats were also observed. The direction of $\hat{A}_{QRS}$ was around $+45°$ when left and around $+120°$ when right bundle branch block was present. In a similar case of Spang,[46] which also showed 3:1 and 2:1 A-V block on other occasions, the right bundle branch block was accompanied by a normal P-R while the left bundle branch block had a prolonged P-R; in this case the histologic changes were more severe in the right branch.

In the case of Holzmann,[23] a slow auricular rate (60 to 70) was usually accompanied by right bundle branch block with a P-R interval of 0.20 to 0.23 sec. Auricular rates exceeding 75 usually brought about partial A-V block with a gradual increase in the P-R intervals of both bundle branch block patterns in each group of conducted beats. Holzmann attributed the appearance of the two bundle branch block patterns to a greater vagal effect on the right branch, or to earlier disappearance of the refractory state, but a later complete restitution of conduction, in the right rather than in the left bundle branch. He thought that the second degree A-V block in this case was caused by a conduction disturbance of Type 1 in the common stem or A-V node but recognized the possibility that it could be caused by bilateral bundle branch block. We shall discuss this case more fully when the mechanism of alternating bundle branch block will be considered.

Although the two following cases do not represent true instances of right and left bundle branch block, the same mechanisms are operative in them as in those previously discussed. In 1923, Stenström[57] reported a case of coupled auricular extrasystoles (Case 4, Figs. 13, 14, and 15) which were conducted with alternate aberration in the right and left bundle branch systems. No differences were observed in the coupling of the two types of aberrant auricular extrasystoles. On the contrary, while the extrasystoles conducted with the right bundle branch block pattern had a normal P-R interval, those conducted with the left bundle branch block pattern had a prolonged A-V conduction time (0.05 sec. or more on the average). According to the explanation of Stenström, this prolongation of the P-R interval in the extrasystoles conducted with left bundle branch block was due to prolonged conduction not in the A-V node or main bundle but in the right branch. In a case of A-V dissociation with interference reported by Burchell,[11] the interference beats displayed four different types of conduction, according to the relation of the P

waves to the preceding R waves. When the former appeared immediately after the latter, the stimulus was not conducted to the ventricles; as the R-P distance increased, some of the P waves were conducted with a P-R interval of 0.39 to 0.50 sec. and a left bundle branch block configuration, then with a P-R interval of 0.23 to 0.29 sec. and a right bundle branch block and finally with a P-R interval of 0.22 sec. and normal ventricular complexes. The author explains this sequence by assuming that the recovery of conductivity starts earlier but proceeds slower in the right than in the left bundle branch, and that partial right bundle branch block is present in the beats which are conducted with the left bundle branch block type.

Some reported cases in the literature which were considered as showing "delayed conduction through both branches" were in reality cases of complete A-V block with varying idioventricular complexes or cases of auricular fibrillation with a high degree of A-V block, and ventricular escapes and fusion beats. In papers published by Korns[29] and by Alvarez and co-workers,[2] most cases of this type have been reviewed. Other cases are those of Mathewson[36] (Figs. 9 to 14) and Bain[6] (Figs. 8 and 9). It is now generally accepted that in cases of complete A-V block with varying ventricular complexes these are due not to intermittent conduction through each of the branches of the His bundle but to changes in the location of the ventricular pacemaker.[70]

In 1929, Barnes and Yater[8] reported a case in which left bundle branch block seemed to be present in one electrocardiogram while another one, recorded after an episode of paroxysmal tachycardia, apparently showed right bundle branch block. The P-R interval was 0.20 sec. in the former and 0.24 sec. in the latter case. They interpreted the case as an alternation of incomplete right and left bundle branch block. While this interpretation may be correct, we believe that simple changes of the heart position (verticalization of the heart) could have been responsible for the changes. Unfortunately, the absence of precordial leads does not permit a definite diagnosis in this case. At any rate, the change in the duration of the P-R interval would be in keeping with the expected changes in A-V conduction when bilateral bundle branch block is present.

In a paper on intraventricular conduction disturbances in acute coronary occlusion, Master and co-workers[35] reported two cases which, according to their opinion, showed atypical right and left bundle branch block with changes in the P-R interval in successive electrocardiograms (Case 4, Fig. 1 and Case 26, Fig. 8). This interpretation is doubtful, as myocardial infarction may be accompanied by widening of the QRS complex due to the so-called "peri-infarction block" and as multiple precordial leads which could have substantiated the diagnosis were not taken.

The most unusual case of what seemed to be an association of an A-V conduction disturbance probably located in the A-V node with a latent conduction disturbance in both branches was published by Kisch and Grishman[27] in 1944. On admission the patient's electrocardiogram showed 3:1 and 4:1 A-V block and the QRS complexes were normal, indicating normal conduction through both branches. An electrocardiogram recorded five minutes after subcutaneous injection of 0.5 mg. of Adrenalin (Fig. 2,*A*) revealed 3:1 A-V block with alternation between normal intraventricular conduction and right bundle branch block (2:1 right bundle branch block). After intravenous injection of 1 mg. Atropine sulfate the following sequence was observed. At fifteen seconds, 3:1 A-V block was still present, but as the auricular rate was now much faster, all the ventricular complexes were of the right bundle branch block type. At thirty-five seconds, the auricular rate was even faster, 2:1 A-V block was present and now the ventricular complexes showed left instead of right bundle branch block. Ventricular extrasystoles and ventricular escapes were also present. At fifty seconds, the ventricular escapes were numerous, interrupting the continuity of the basic rhythm in such a way that now only every fifth P wave was conducted to the ventricles with a right bundle branch block pattern. (As the ventricular escapes had a fixed coupling to the preceding beat and appeared usually separated from each other by equal intervals, the authors mistakenly considered them as indicating a parasystolic rhythm.) On one occasion, the fourth P wave was conducted with a left bundle branch block ventricular complex.

The 4:1 A-V block with normal ventricular complexes, present at rest in this case, could be explained by assuming 4:1 block in both bundle branches, with conduction occurring at the same time in both branches. However, the probability of such a coincidence is so small that the A-V

conduction disturbance in this case must be attributed to 4:1 block in the A-V node or the common stem, and the bundle branch block pattern to an independent conduction disturbance in the branches. That under the influence of Atropine right bundle branch block was present at first, while left bundle branch block appeared later, means that the conduction disturbance in the right bundle branch must have decreased, either because this branch was more affected by the vagus than the left branch, or because it showed a supernormal phase of conductivity while the left branch did not. In this case, both the right and the left bundle branch block patterns appeared only when the auricular rate became faster after injection of Adrenalin or Atropine; this is not unusual in bundle branch block. On the contrary, the A-V conduction improved under these conditions. It is well known that in cases of partial A-V block, when the auricular rate is increased through procedures or drugs which increase the sympathetic or diminish the vagal tone, conduction improves in some cases and becomes worse in others. It is quite possible that in many of the latter cases, the cause of the A-V block was bilateral bundle branch block, especially if the conducted beats already show block in one of the branches. This would be in accordance with the generally accepted belief that the vagus has no direct influence on the ventricles; in the presence of bilateral bundle branch block it is to be expected that any of these procedures or drugs would only impair conduction even more because of the increased heart rate. In our Case 1, for instance, A-V conduction became definitely worse after exercise. In cases of partial A-V block with a bundle branch block pattern, exercise or Atropine might be a useful test to determine if the A-V conduction disturbance is located in the A-V node or in the other branch.

It follows from the preceding that cases in which the electrocardiogram can be considered to prove the presence of bilateral bundle branch block beyond any doubt are exceedingly rare, since we have not been able to find more than seven cases of this kind in the literature. This does not by any means signify that bilateral bundle branch block is uncommon. Quite to the contrary, the actual great incidence of either right or left "complete" or "incomplete" bundle branch block makes it the more likely that both should coexist in a large number of clinical cases. Supporting facts for this contention are the high incidence of bilateral bundle branch lesions in histologic studies and of a bundle branch block type of ventricular complexes in complete A-V block, as well as the fact that in bundle branch block the association of A-V conduction delay seems to be more frequent than could be expected as a matter of coincidence.[13] Unfortunately, in most instances of bilateral bundle branch block the diagnosis cannot be made with certainty. When the block is complete in both branches, a pattern of complete A-V block which results is indistinguishable from that produced by lesions of the main bundle and A-V node (see introduction). If there is complete block of one of the branches and incomplete block of the other one, the electrocardiogram will show a bundle branch block pattern due to the former, with A-V conduction disturbances due to the latter. Many of the cases of bundle branch block with prolonged P-R intervals, which are not infrequent in clinical electrocardiography, are produced by this mechanism, but it is impossible to differentiate them from cases of partial A-V block, localized in the main bundle with coexistent bundle branch block. Such a diagnosis becomes possible only if the degree of block in one of the branches is less than in the other on some occasions and greater on others. The contralateral bundle branch block pattern will then appear, accompanied by changes in the P-R interval. This happened in the two cases presented in this paper, as well as in the seven cases reported in the literature.

Of the nine cases in which the diagnosis of bilateral bundle branch block was considered certain, seven showed alternating right and left bundle branch block at some time. We have ascribed this pattern either to alternating 2:1 right and left bundle branch block, or to 2:1 block in one of the branches in the presence of a constant prolongation of conduction in the other branch. The first explanation appears less probable, as it would necessitate a coincidence not only of the same type of block in two anatomically widely separated structures, but also the occurrence of conduction in one branch only while the other shows block; otherwise 2:1 A-V block with normal interventricular conduction would result. The second explanation appears more likely, and it could be actually shown to apply in one of the published cases in which the beginning of the alternating bundle branch block patterns was registered.

In Fig. 3 of Holzmann,[23] P-P intervals of 0.92 to 1.00 sec. were accompanied by 1:1 conduction with a right bundle branch block pattern (QRS, 0.10 sec.) and P-R intervals of 0.28 to 0.30 sec. We assumed that in this case the left P-R interval was about 0.30 sec. while the right P-R interval was more than 0.40 sec., so that the right ventricle was activated entirely by way of the left bundle branch. After a P-P interval of 0.90 sec. the P-R interval became 0.35 sec. In order to explain the following events, we assumed that at this time the left P-R interval was 0.35 sec. while the right P-R interval became infinite. As the right ventricle was activated from the left bundle branch in previous beats, this would not have caused any change in the configuration of QRS. The next P-P interval was 0.79 sec., followed by a left bundle branch block pattern with a QRS duration of 0.16 sec. and a P-R interval of 0.21 sec. We assumed that because the right bundle branch was not activated at all in the preceding complex, and therefore had a long diastolic recovery period, the right P-R interval was now 0.21 sec. while the left P-R interval was 0.35 sec. as in the previous complex or even longer; this caused the left ventricle to be activated entirely from the right bundle branch. From this point on, the auricular rate continued faster than previously, and an alternating right and left bundle branch block pattern became established.

The main feature responsible for the appearance of alternating right and left bundle branch block patterns is, accordingly, the presence, in one bundle branch, of a short relative refractory phase which causes 2:1 block to appear suddenly when the auricular rate increases, while the other branch has a long relative refractory phase, so that the same increase in the heart rate leads only to a progressive increase in conduction time. Because of the failure of one bundle branch to respond to one auricular stimulus, the conduction time in this branch during the next stimulus is considerably shorter than previous to the appearance of a dropped beat, so that the conduction disturbance of the other branch, which was previously manifest only as a prolongation of the P-R interval, now manifests itself as a contralateral bundle branch block pattern.

A case in which right and left bundle branch block patterns were present in the electrocardiograms of the same patient without disturbances of the A-V conduction is described in a paper by Kurtz[30] (Case 5). After an acute episode of posterior myocardial infarction, right bundle branch block was present; one month later the intraventricular conduction was normal; after three years another tracing showed left bundle branch block which again disappeared 10 months later. On these four different occasions, the P-R interval was normal. The absence of A-V conduction delay when left bundle branch block was present is

clearly due to the fact that the previous right bundle branch block had receded completely. This case can therefore not be considered as showing bilateral bundle branch block. This applies also to the case of Folli and Libretti.[19a]

The problem of "partial," "incomplete," or "transient" bundle branch block is fundamentally related to the cases of bilateral bundle branch block discussed in this article. While to comment upon it at length would be outside the scope of this paper (for this purpose many comprehensive articles and reviews can be consulted),[15,41,45,52,74] a few considerations are worth while.

As in the case of atrioventricular block, bundle branch block can be either permanent or nonpermanent. The latter type can be subdivided into two general groups. In the group of "variable" or "unstable" block, this appears intermittently or as partial (2:1, 3:1, etc.) bundle branch block, or there are repeated transitions between normal and abnormal intraventricular conduction. This situation may persist for long periods of time.[42,52,67] Usually the final result is the establishment of permanent bundle branch block, although on rare occasions normal intraventricular conduction may become permanent. There is a definite relationship between this type of unstable bundle branch block and the heart rate, and critical rates have been described, above which the block is present while at slower rates intraventricular conduction is normal, or less abnormal.[54,64-7] In rare instances conduction became normal only after a short diastolic pause, presumably due to a supernormal phase of conduction.[52] The cases of unstable bundle branch block can be explained by assuming that the prolongation of the relative refractory period which contributes to the conduction disturbance is so small that the normal variations of the heart rate are sufficient to make the block appear and disappear. In addition to the influence of the heart rate, spontaneous and unpredictable changes in conductivity may determine whether or not bundle branch block will be present at a given time; this is shown by the fact that in numerous cases the critical heart rate was found different at different times.[12,52,54] Similarly, in partial A-V block the degree of conduction disturbance will change sometimes according to the rate and sometimes spontaneously.[74] The left bundle branch block of our Case 1 belonged to this type, as the unstable conduction disturbance in this bundle branch was present during the 30 months period of electrocardiographic observation.

In the second group of cases, that of "temporary" bundle branch block, the prolongation of the refractory period in the bundle branch is apparently of such a magnitude that normal variations of the heart rate are unable to produce any changes in the electrocardiographic pattern during the period when block is present. In these cases the block usually does not last more than a few days or weeks, although cases have been described in which bundle branch block disappeared after it was present for years.[25,38,45,52] In many of these cases the appearance and disappearance of the block can be correlated with some particular clinical condition, but in some the changes occur without any apparent cause to explain them. One of the clinical conditions which more frequently can give place to this type of temporary bundle branch block is myocardial infarction and related conditions.[1,35,48,71,72,74] The transient right bundle branch

block present in electrocardiogram 6 of our Case 1 can be included in this second group and its occurrence during the time when electrocardiographic abnormalities indicating a possible myocardial infarct with septal involvement were present affords a good explanation for its rapid appearance and disappearance.

While these two groups of "unstable" and "temporary" bundle branch block can be considered as separate entities from a clinical or electrocardiographic point of view, the distinction may not be as clear-cut concerning their pathogenesis. In fact, although this is difficult to prove, it is quite possible that at least in some of the cases of "temporary" bundle branch block the conduction was never completely interrupted, and that these cases would have become unstable if the heart rate had been slow enough. A simple prolongation of the conduction in one of the bundle branches is enough to produce the pattern of "complete" bundle branch block when it exceeds 0.04 to 0.06 sec. It is quite understandable that such a block is more likely to regress than one produced by complete interruption of conduction, in the same way as first degree A-V block can disappear more easily than complete A-V block. This is supported by reported cases in which carotid sinus massage was able to elicit normal intraventricular conduction even when permanent and definitive bundle branch block seemed to be present.[27,40,54] Perhaps the most impressive of these observations is the one reported by Alzamora-Castro and co-workers,[3] who in this way could induce normal conduction in seven cases of "permanent" right and in four of "permanent" left bundle branch block. It is logical to assume that if the heart rate could be slowed enough, many cases of apparently permanent bundle branch block would prove to be due to delayed and not interrupted conduction in the affected branch.[45] This could have been the case, for instance, in the right bundle branch block present in electrocardiogram 6 of our Case 1.

Many authors,[21,22,55,57,58,59,70] especially in the older literature on the subject of incomplete or partial bundle branch block, compared the possible different degrees of conduction disturbances in the branches with the well known different degrees of A-V block. This practice has been almost abandoned, possibly because of the impracticability to apply it to the common instances of bundle branch block in current electrocardiography. However, the fact that the electrocardiogram does not detect the existence of various degrees of impaired conduction in the branches, except on comparatively rare occasions, does not mean that they are infrequent.

There are three fundamental varieties of A-V block: (1) First degree or "incomplete" A-V block, consisting in a simple prolongation of the P-R interval, usually of a constant duration. (2) Second degree or "partial" A-V block, characterized by the presence of dropped beats. Two subgroups are recognized here (a) dropped beats through the formation of Wenkebach periods (Type I of Mobitz), and (b) dropped beats of sudden occurrence (Type II of Mobitz). (3) Third degree or "complete" A-V block, consisting in complete interruption of the A-V conduction. The first two varieties are far more frequent than the third. The experimental and clinical observations discussed in this paper show that the same types of conduction disturbance as in A-V block may occur in bundle branch block. In this case, as in that of A-V block, incomplete block has been

now recognized as more frequent than the corresponding forms of complete bundle branch block.[62] These cases are the counterpart of first degree A-V block, and as in the latter, the delayed conduction in the affected branch is usually of constant duration.

The bundle branch block counterpart of second degree A-V block is furnished by the now not uncommon cases of variable bundle branch block. The reason for its comparatively less frequent presence in clinical electrocardiography is inherent in the anatomic peculiarities of the conduction system. This was expressed as early as 1927 by Stenström:[59] "In bundle branch block, where the septal muscle conducts the impulse of contraction from one side to the other, the margins, between which the conduction times in one branch through their variation can produce gradual changes in the ventricular curve, are much closer. It is determined by the time of passage through septum and in fact a prolongation of the conduction time of about 0.05 sec. must be enough to make the impulse, retarded in the impaired branch, ineffective, because its ventricle gets activated from the contralateral side. In the electrocardiogram this evokes a completely aberrant ventricular complex of the same features as in complete block in the branch. . . . From the reasons just mentioned the most common electrocardiographic signs of a bundle branch block of the second stage must be a periodic variation between normal or nearly normal and completely aberrant ventricular curves."

Let us take as an example, Type I second degree block, which would lead to Wenckebach's periods in the case of the A-V node. In cases of this type, the first P-R interval after the dropped beat is shorter than all others, but in many cases it is still prolonged. If this type of block were to appear in one of the bundle branches, the bundle branch block pattern would be present constantly in spite of the occurrence of Wenckebach's periods in the bundle branch, as the blocked ventricle would then be constantly excited from the other bundle branch regardless of the actual conduction time in the diseased bundle. If the conduction time after missed conduction were completely normal, the bundle branch block pattern would be interrupted at regular intervals by normal conduction. Some of the reported cases of 3:1 and 4:1 bundle branch block[55] could have been caused by this mechanism. If the prolongation of conduction after failure of conduction is less than 0.03 to 0.05 sec., the pattern of complete bundle branch block would be interrupted by that of incomplete block. Cases of this type are occasionally seen in clinical electrocardiography. Similarly, Type II bundle branch block could be present in spite of a permanent pattern of bundle branch block in the electrocardiogram.

It is evident from the preceding considerations that there is no way to tell when conduction is completely interrupted in one of the branches. The reported cases in which apparently complete bundle branch block was present in the electrocardiogram without a histologic interruption of the bundle branch having been found at autopsy[43,44] could be explained on this basis since only a prolonged conduction in the branch could have been present. It is surprising that the possibility of first degree bundle branch block as a cause of the typical pattern of complete bundle branch block is not even mentioned in the common textbooks on electrocardiography, with a single exception.[31]

Under the name of "bilateral intraventricular block" Segers and Enderle[53] reported a series of cases characterized by a delayed intrinsicoid deflection in both right and left precordial leads. Two similar cases were reported by Boyadjian and VanDooren[9] and similar single instances were previously published by Segers and associates.[49,50] The fact that in these cases the P-R interval was normal was used as an argument in favor of the hypothesis held by Segers[51] that the common patterns of bundle branch block are produced by lesions localized not in the branches of the His bundle but in the walls of the ventricles (intraparietal block).

We believe that the type of cases referred to by the aforementioned authors represents a true "bilateral intraparietal block", or, more probably, the association of true bundle branch block with intraparietal block of the contralateral ventricle. Actually, we have ourselves many times observed cases of typical right bundle branch block associated with intraventricular conduction disturbances in the wall of the left ventricle, always in patients with heart disease especially involving the left ventricle (hypertensive and coronary heart disease), and with remarkable frequency in cases of chronic chagasic myocarditis. The existence of intraventricular conduction disturbances localized in the free walls of the ventricles and therefore independent of blockage in the branches is a well known fact,[4,5,19,68] and there is no reason why such an intraparietal block cannot be associated with true bundle branch block of the same or the contralateral ventricle. In this latter case, the intrinsicoid deflection can be delayed in both right and left precordial leads, and the P-R interval does not necessarily have to be prolonged. True bilateral bundle branch block, like that present in all the cases reviewed in this paper, must prolong the A-V conduction time. The intrinsicoid deflection in precordial leads, in our two cases, was delayed only on the side of the chest corresponding to the branch showing the greater degree of block in this particular moment, and it was within normal limits on the opposite side. The same situation was true in the cases of Dressler[16] (Case 2) and of Burchell[11] (in the other reviewed cases precordial leads were not taken or reproduced in adequate number). In bilateral bundle branch block, the form of QRS is determined by the branch which shows the greater degree of blocking; the delayed conduction in the other branch does not affect the shape of QRS but prolongs the A-V conduction time.

During the review of published cases we have deliberately omitted some cases (Katz and associates,[26] Strauss and Langendorf,[61] Dressler's[16] Case 1, Scherf and Boyd,[47]) which are intimately related to the problem of bilateral bundle branch block and some of which, in fact, may be true instances of that condition. In all of them, two different forms of intraventricular conduction patterns were present, with a wide QRS and with different forms of A-V conduction disturbances. Actually, these cases were considered by their authors as showing alternate or intermittent conduction through each of the branches of the His bundle. However, these cases were also characterized by some peculiar facts which do not seem to fit well into the common forms of bundle or intraventricular conduction disturbances. One of these facts was a change of about 180° in the

direction of $\hat{A}_{QRS}$ accompanying the transition from one type of ventricular complex to the other. It is a common observation, which has also been statistically proved, that the appearance of bundle branch block does not change fundamentally the direction of $\hat{A}_{QRS}$,[10,24] and accordingly, in our two cases and in the reviewed cases of bilateral bundle branch block, the passage from right to left bundle branch block or vice versa produced changes in the direction of the $\hat{A}_{QRS}$ no greater than 90° at the most. A second unusual fact was that one of the ventricular patterns showed pronounced right-axis deviation with deep S waves in Lead I and tall R waves in Leads II and III, in patients with hypertensive or arteriosclerotic heart disease, in which the left bundle branch block pattern showed a horizontal heart position. It is unlikely for right bundle branch block to produce this pattern under these conditions. In these cases no multiple precordial leads were taken. In a personal observation of this type, the precordial leads did not show the case to be a typical instance of alternating right and left bundle branch block. So in spite of the close relation of this type of case to bilateral bundle branch block, its peculiar character makes it advisable to consider them separately in a further paper.

SUMMARY

1. An electrocardiographic diagnosis of bilateral bundle branch block can be made in rare instances in which conduction in the branches is not completely interrupted and the degree of block in one of the branches is less than in the other on some occasions and greater on others; this allows the patterns of right and left bundle branch block to appear alternately or intermittently in the same patient, accompanied by changes of P-R. Two personal cases of this sort are reported and seven similar observations from the literature are discussed.

2. While the incidence of bilateral bundle branch block in which this condition can be definitely proved is very small, the great incidence of unilateral bundle branch block makes it probable that many cases of complete A-V block, attributed to a conduction disturbance in the A-V node or the common stem of the bundle, are in reality caused by bilateral bundle branch block.

3. In seven of the nine cases of definite bilateral bundle branch block, alternation of the right and left bundle branch block patterns was present at some time. The most probable explanation of this was considered to be 2:1 block in one of the branches in the presence of a constant prolongation of conduction in the other branch.

4. Conduction in the branches behaves in the same way as in the rest of the A-V conduction system. In one of the cases (No. 1), all the possible forms of impaired conduction were demonstrated to be present in the left branch of the His bundle (simple prolonged conduction time, Wenckebach periods, 2:1 and 3:1 block, and transient complete interruption of conduction).

5. True bilateral bundle branch block must necessarily prolong the A-V conduction time. The form of the ventricular complex is determined by the branch with the greater degree of block, while the conduction delay in the branch in which the block is less important determines the lengthening of the P-R interval. This must be so because the stimulus reaches the ventricles through the less affected branch.

6. In true bilateral bundle branch block the intrinsicoid deflection of the ventricular complex is delayed only on the side of the chest corresponding to the more affected branch and is within normal limits on the opposite side. Cases in which the intrinsicoid deflection is delayed over both ventricles probably represent an association of true bundle branch block with an intraparietal conduction disturbance of the contralateral ventricle.

SUMMARIO IN INTERLINGUA

Multe casos de complete bloco atrioventricular es attribuite a un disturbate conduction in le nodo atrioventricular o in le trunco commun del fasciculo, ben que illos es plus probabilemente causate per bloco de branca bilateral. Sed isto es demonstrabile solo si le conduction in le brancas non es completemente interrumpite e si le grado del bloco in un del brancas es a vices inferior e a vices superior al grado del bloco in le altere branca. Sub iste conditiones il es possibile pro le complexos del dextere e del sinistre bloco de branca manifestar se alternante- o intermittentemente in le mesme patiente, accompaniate per alternationes de P-R. Le forma del complexo ventricular es determinate per le branca con grado superior de bloco, durante que le retardate conduction in le altere branca determina le allongation de P-R. Es reportate septe tal casos ab le litteratura e duo ab nostre experientia personal. In un de iste ultime casos nos demonstrava in le branca sinistre del fasciculo de His simple prolongation del tempore de conduction, periodos de Wenckebach, bloco 2:1 e 3:1, e transiente interruption complete del conduction.

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THE DIAGNOSTIC ACCURACY OF Q_3 AND RELATED ELECTROCARDIOGRAPHIC ITEMS FOR THE DETECTION OF PATIENTS WITH POSTERIOR WALL MYOCARDIAL INFARCTION

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INTRODUCTION

A DIFFERENTIATION between normal and abnormal should be made on the basis of the distribution of a diagnostic item in normal population and in a population of patients. However, the number of studies of normal distribution of electrocardiographic items is quite small in view of the large electrocardiographic literature, and, to the best of our knowledge, no adequate statistical investigation of the frequency distribution of any electrocardiographic item in one or the other category of patients has yet been made. Frequently, entirely arbitrary criteria were suggested for differentiation between normal and abnormal, resulting in a rather large proportion of diagnostic errors, as will be shown in this study.

Improvement of the diagnostic differentiation can be made by a more precise definition of normal groups as to age, body build, relative body weight, etc., and by better standardization of procedure.[1-4] This reduces, but does not eliminate, the overlap in the distribution of electrocardiographic items in normal population and in patients, on which their diagnostic separation depends. In providing data of normal and abnormal distribution of several electrocardiographic items, it was possible to evaluate more precisely their diagnostic significance by means of a simple statistical procedure.[5] We chose for this analysis the Q wave in Lead III and several related items. A prominent Q_3 is a typical feature of posterior wall myocardial infarct, but it also may be found in persons without evidence or history of heart disease. For this reason, the significance of a prominent Q_3 has been the subject of a rather large literature.

Pardee[6] suggested as a normal limit for Q_3, a ratio of under 25 per cent of the maximum R wave in any standard lead, in the absence of right-axis deviation or an M or W type complex. Bayley[7] subsequently found in 163 cases a high incidence of coronary artery disease when the duration of Q_3 was equal to or greater than 0.04 sec. The criteria of a Q/R ratio of less than 25 per cent and

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This investigation was supported (in part) by research grants H-10 (C6 and C7) from the National Heart Institute, of the National Institutes of Health, Public Health Service, and from the Minnesota Heart Association.

Received for publication Dec. 27, 1954.

a Q duration of less than 0.04 sec. have more recently been extended to the left leg and esophageal leads as an indication of normality.[8,9] These suggestions were made without adequate statistical analysis, but they have been used as criteria for analysis of a smaller or larger abnormal, normal, or mixed material.[10-12]

As a rule the results were expressed in terms of percentage distribution in relation to the above limits. While this has a bearing on the distribution of a prominent Q_3, such evaluation is far from adequate. Another objection against some of the publications is the vague definition of normal and abnormal groups. The comparison of normal and abnormal has often been made with markedly different age groups. In several earlier reports[10,13] arterial hypertension was shown to be frequently associated with a prominent Q_3. Yet this relationship is quite obscure since an abnormal Q_3 is absent in the majority of patients with uncomplicated arterial hypertension.

Myocardial infarction of the posterior wall is the only condition, well substantiated by autopsy, which will produce a prominent Q_3 in the great majority of cases. It is clear that this group will show the best diagnostic significance of a prominent Q_3 for detection of abnormality, and that in all other abnormal conditions the diagnostic value, if anything, will be poorer.

In a recent posterior wall myocardial infarct, Q_3 is not the only diagnostic criterion and a safe interpretation can be made even when Q_3 does not meet Pardee's and Bayley's critical values: Diagnostic difficulties arise mainly in old posterior wall infarct, where a prominent Q_3 may be the only residuum. Therefore, we compared three phases of posterior wall infarct: the first two weeks (acute), 1 to 3 months (subacute), and 6 months or more (chronic). In this respect, our series differs from earlier studies.

Another difference is the selection of the normal group. We compared the infarct group not with a random sample of normal population, but with those individuals with a Q_3. This is a preselected normal group, but it is that group from which patients with myocardial infarct have to be differentiated. The problem of the significance of a prominent Q_3 does not arise if it is absent, as is the case in most normal persons. Since the size of the normal group from which these cases were selected is known, the incidence of Q_3 for normal population comparable to our group can be estimated.

MATERIAL

Normal Group.—The normal group was selected from two sources: (a) Thirty-seven from a group of 185 normal middle-aged men between 47 and 57 years, and fourteen from a group of 118 normal young men between 18 and 25 years. These groups were investigated annually at this Laboratory; the older age group over an interval of 7 years and the younger age group over a span of 3 years. In addition to a thorough clinical examination, numerous laboratory procedures such as ballistocardiography, 6-foot radiographs and fluoroscopy, kymography, photoelectrokymography, vectorcardiography, blood lipids, body composition, etc. were applied, and the response to various physiologic stresses was also investigated. Only individuals were selected who were normal according

to all these criteria at the first investigation and stayed normal over an interval of 3 (younger group) or 7 (older group) years. We are aware that autopsy may reveal in some of these individuals, particularly in the older age group, myocardial lesions,[14] but believe that this normal group is as good as can be obtained without autopsy.

(b) The second group consisted of thirty-nine patients with a prominent Q_3 and with various diagnoses, whose myocardium was found to be macroscopically and microscopically normal at autopsy, as selected from approximately 1,300 autopsy records of the Minneapolis Veterans Administration Hospital.

Thus the total normal group consisted of 90 tracings, 14 from clinically healthy males between 18 and 25 years, thirty-seven normal males between 47 and 57 years, and thirty-nine autopsied cases with known normal myocardium from 25 to 75 years. The mean age of the latter group was 53.5 years, four were below 40 years.

Since Q_3 in an appreciable number of patients with posterior wall myocardial infarct was under 25 per cent of the maximum R wave or shorter than 0.04 sec., Pardee's or Bayley's criteria could not be used as a basis for the selection of our normal group. In the great majority, the Q wave was quite large, but some normal individuals with smaller Q waves were included corresponding to the situation in the group of patients. The criteria for the selection of the normal group can best be seen in the frequency distribution curves in Figs. 1 to 5, which include cases from a Q_2/R maximum ratio of 12.5 per cent up, and from a Q_3 duration of 0.025 sec. up.

Abnormal Material.—Cases with fresh posterior wall myocardial infarct, with typical S-T elevation in Leads II, III, and aV_F, and following typical evolution in serial ECG tracings, were selected from the files of the Veterans Administration Hospital, Mt. Sinai Hospital, and University Hospital, Minneapolis. All patients showed also definite clinical evidence of acute myocardial infarct. Cases with bundle branch block, intraventricular block, or idioventricular pacemaker were excluded. In eighteen cases, autopsy records were available; they were confirmatory in all. If possible, for each patient one tracing was selected from the acute phase (1 to 14 days after the infarct), one for the subacute (1 to 3 months), and one from the old (healed) stage (over 6 months). Unfortunately, records for the last phase were not available in all patients. In order to make the number of patients for this phase quantitatively comparable, we added tracings of thirty-eight patients (47 per cent of the total of 80 cases) with QRS and T patterns typical for healed posterior wall infarct, and with a substantiating clinical history. We are aware that such ECG's are not as diagnostic as serial tracings, but autopsy was confirmatory in all eight cases of this group in whom it was performed. A total of 150 patients with posterior wall infarct was obtained with 83 tracings in the acute phase, 72 tracings in the subacute, and 80 tracings in the chronic stage.

METHODS

The majority of electrocardiograms used in this study were recorded on either Sanborn or Cambridge direct-writing machines. The tracings were analyzed for the following items: (1) Total QRS duration; (2) Intervals—in Leads II, III and aV_F: total duration of the Q wave (Q interval), time from onset to peak of Q wave (Q-peak interval), and time from onset of QRS to peak of R wave (R-peak interval). (3) Amplitudes: Q, R and T wave in Leads II, III and aV_F; and height of the maximum R in any standard lead. (4) Ratios: Q amplitude in Lead III to R maximum of any standard lead, Q amplitude in aV_F to the R amplitude in aV_F. A total of twenty-two items was therefore analyzed from each ECG.

Because of minor variations of duration and amplitude in successive QRS complexes, the measurements of at least three successive QRS complexes were averaged. Measurements of duration were recorded to the nearest 0.005 sec. and amplitudes to the nearest 0.2 mm. The error of measurement was determined by independent repeat measurements and was found to fall within the 90 per cent range limits of a previous study,[15] i.e., within $\pm$ 0.0058 sec. for the QRS duration in the standard leads, within $\pm$ 0.15 mm. for the R amplitude, and within $\pm$ 0.17 mm. for the T amplitude.

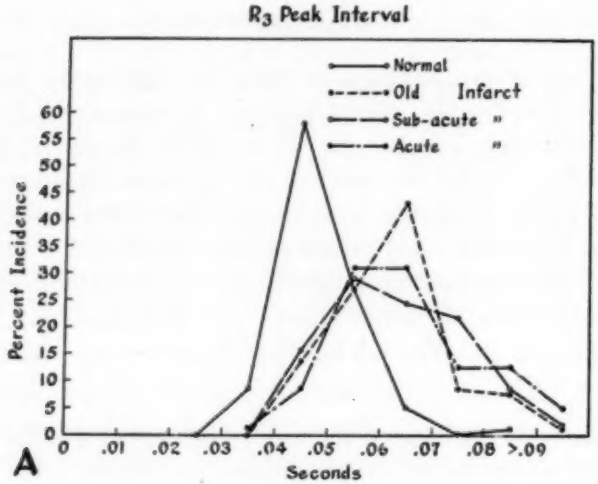
RESULTS

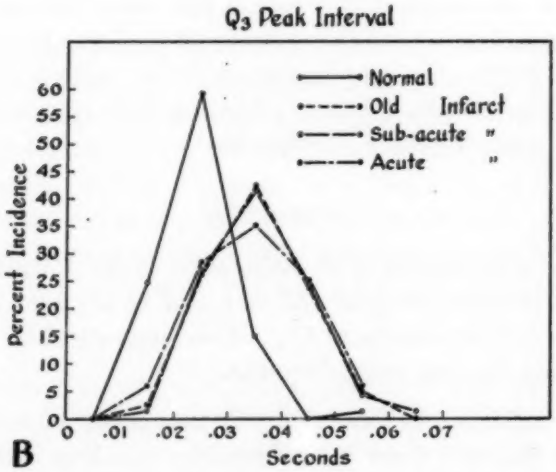
Incidence and Distribution of Prominent Q_3 in the Normal Groups.—Twenty per cent of the total older group of 185 men and 12 per cent of the total younger group of 112 men had a prominent Q_3. This suggests that with increasing age a prominent Q_3 may become more frequent.

The greater incidence (12 per cent) in our group of normal young men as compared to that (0.5 to 1.6 per cent) found by previous investigators[6,11,21,22,25-27] in similar normal age groups is largely explained by the different criteria for selection. The earlier workers used Pardee's criteria, but since it was one of the purposes of this study to examine their validity, they could not be taken as the basis for selection of our sample.

There was no significant difference in the distribution of the Q_3 amplitude between younger and older men who had a prominent Q_3, but the Q_3/R maximum ratio exceeded 25 per cent in four out of fourteen young men and in twenty-six out of thirty-seven older men. This was due to a smaller R maximum in the older men. Seventy-nine per cent of the younger normal men with a prominent Q_3 and 18 per cent of the older men had an R maximum exceeding 10 mm. We are aware that differences in the distributions within such small groups have only limited value, but they are confirmatory to age trends in larger groups.[2]

In no other item was there any significant difference in the distribution between younger and older men. Therefore, the age groups were pooled for statistical analysis.





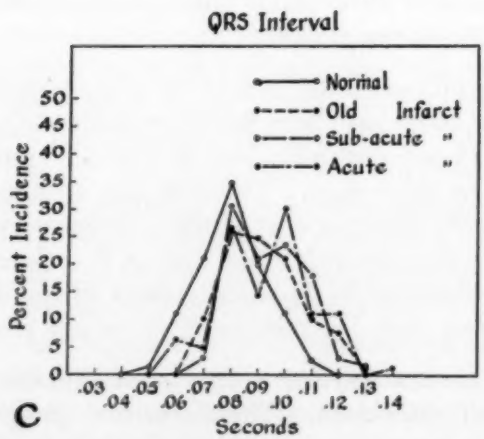


Fig. 1.—Frequency distribution (ordinate: incidence in per cent) in normal population, and in patients with posterior wall myocardial infarct (acute, subacute, old), of the QRS interval (*C*), of the Q_3 peak interval (*B*), and of the R_3 peak interval (*A*).

QRS Interval.—The means and standard deviations of all items with symmetric distribution curve are listed in Table I. Means and standard deviations have been calculated only for the old infarct group because, for the majority of items, only slight differences exist among the distributions at each stage of infarction (Figs. 1 to 5). The significance of the difference between the means was determined by the *t* test.

TABLE I. MEANS AND STANDARD DEVIATIONS (S.D.) OF ITEMS WITH SYMMETRIC DISTRIBUTION FOR 90 NORMALS AND 80 PATIENTS WITH OLD POSTERIOR WALL INFARCT, AND STATISTICAL SIGNIFICANCE (*t* test) OF THE DIFFERENCES BETWEEN NORMALS AND PATIENTS

	INTERVALS								AMPLIT.
	QRS	Q_2	Q_3	Q_{aVF}	Q_3 PEAK	Q_{aVF} PEAK	R_3 PEAK	R_{aVF} PEAK	Q_3
Normals									
Mean	.079	.023	.032	.028	.022	.018	.044	.042	2.69
S.D.	.014	.004	.005	.006	.005	.003	.008	.008	1.40
Infarcts (old)									
Mean	.091	.031	.044	.039	.032	.025	.058	.053	4.87
S.D.	.016	.007	.009	.008	.008	.007	.011	.011	2.74
t value	5.45	7.34	9.69	9.17	9.26	6.97	9.33	7.21	.032
Significance level	.001	.001	.001	.001	.001	.001	.001	.001	none

The distribution of the QRS interval at each infarct stage as compared to the total normal group is illustrated in Fig. 1, *C*. The normal mean for QRS duration of 0.079 represents a highly significant difference from the mean value of 0.091 for the old posterior infarct group.

The range of normal values extended from 0.05 to 0.11 sec. and that of the old infarct group from 0.06 to 0.14 sec.

Q Interval—Leads II, III, and aV_F.—Means and S.D. for each item are listed in Table I, and the distribution is shown in Fig. 2. Although the *t* test reveals a highly significant difference between the means of the normal and the infarct group in each item, the distribution curves, nevertheless, reveal considerable overlapping.

The normal values of the Q interval extend to 0.035, 0.06, and 0.05 for Leads II, III and aV_F, respectively, but may be as small as 0.015 sec., 0.02 sec. and 0.015 sec. in old infarcts. This distribution is not compatible with the normal upper limit of 0.04 for Q_3 in Graybiel and associates' textbook[16] and even less so with the upper normal limit of 0.03 in Burch and Winsor's textbook.[17] However, it agrees fairly well with the distribution in the combined material of Myers and Oren,[9] and Rubin and associates,[12] amounting to eighty-nine cases with posterior wall infarct and fifty-eight normals. In 56 or 62 per cent of those with posterior infarct the Q_3 interval was 0.04 sec. or less, while 9 or 15 per cent of the normals had Q_3 greater than 0.04 sec. Fiske[18] found in 3 out of 12 ECG's with posterior infarct confirmed by autopsy, a Q_3 interval under 0.04 sec.

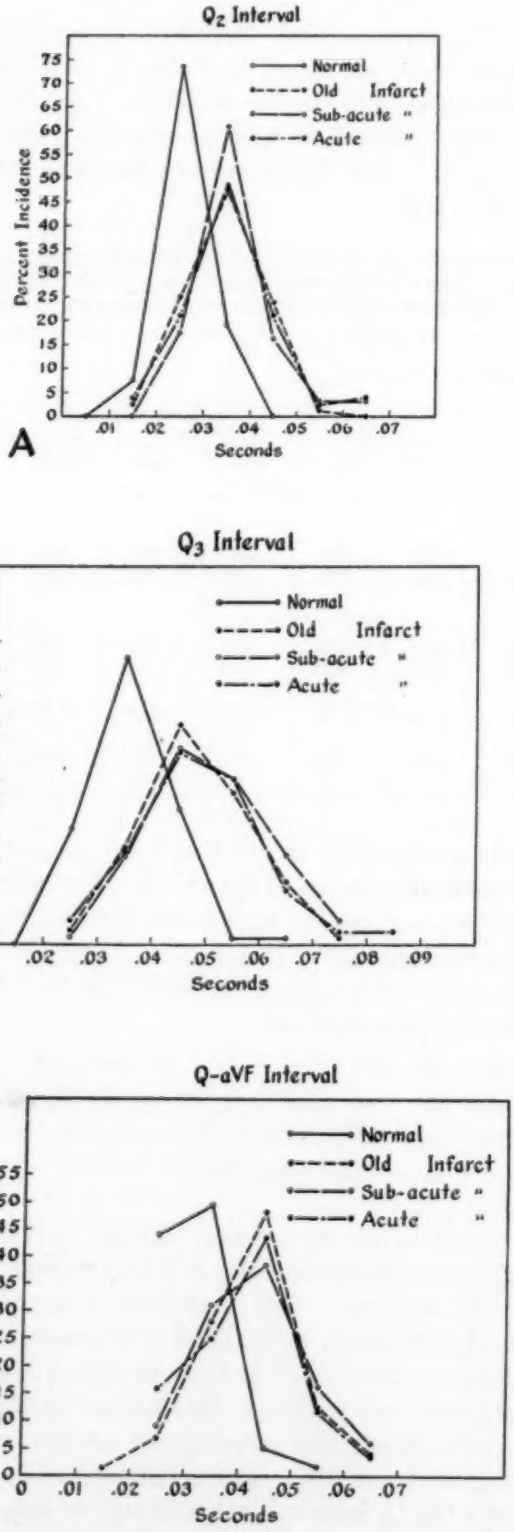


Fig. 2.—Frequency distribution (ordinate: incidence in per cent) in normal population, and in patients with posterior wall myocardial infarct (acute, subacute, old), of the Q_2 interval (*A*), of the Q_3 interval (*B*), and of the Q_{aVF} interval (*C*).

In our material, the duration of the Q_{aVF} interval was equal or greater than 0.04 sec. in 4 (7 per cent) of 59 normal tracings and in 64 per cent of the old posterior infarct tracings in which it was present. This agrees fairly well with Barker,[19] and Graybiel and associates.[16] However, Myers and Oren[9] found only three of their twenty-five infarct cases with Q_{aVF} to exceed 0.04 sec. and in two cases of old infarct it was absent. None of their twenty-five normals and only one of thirty-three normals studied by Rubin and associates,[12] had a Q_{aVF} equal to or greater than 0.04 sec. In one patient of our group in which serial tracings were available, a Q_{aVF} present during the acute phase of a posterior wall infarct had disappeared in a follow-up tracing taken 1 year and 4 months later.

In five of our patients a prominent Q_2 was present in the acute phase of infarct but disappeared later. This agrees with Nyboer's opinion[20] that Q_2 is absent in 25 per cent of posterior infarct tracings and considerably decreases its diagnostic value. The degree of overlapping between normal and old infarct is greatest in the Q_2 interval, and smallest in the Q_{aVF} interval (Fig. 2).

Q Peak—Leads II, III, and aV_F.—These intervals are defined as the duration from onset of QRS to the nadir (or peak) of the Q wave. Means, standard deviations, and statistical significance are shown in Table I, and the distribution for the Q_3 peak interval in Fig. 1,*B*. Although the *t* test reveals significant differences between means, the distribution curves again show considerable overlapping. For the Q peak interval in Lead II the distribution data were almost identical for normal and infarct groups; therefore, this material was not further analyzed.

R Peak Interval—Leads III and aV_F.—The interval from onset of QRS to peak R wave is mentioned by Barker[19] as an important diagnostic item, although no statistical data were given. The mean values for the R peak interval in Lead III and aV_F are listed in Table I, and the distribution for the R_3 peak interval is shown in Fig. 1,*A*. Only slight differences of distribution exist among the three infarct stages. The overlapping between normal and infarct is not as large as with other items. Sixty per cent of the old infarct tracings and only 6 per cent of the normal group had an R peak duration in Lead III equal to or greater than 0.06 sec. The R peak interval in Lead aV_F does not offer as good a differentiation as in Lead III, mainly because of the large number of infarct tracings (62 per cent) in which it was equal to or less than 0.05 sec. On the other hand in only two normals (2.7 per cent) was the R peak interval in aV_F longer than 0.05 sec.

Q Amplitude—Leads II, III and aV_F.—The distribution curves for the Q amplitude in each lead (Fig. 3,*A* to *C*) are skewed and show only slight differences among the three phases of posterior infarction. Only Lead III shows some difference in the distribution of the normal and infarct groups, but the difference between the means of the normal and old infarct group was statistically not significant (Table I). It is unlikely, therefore, that adequate separation of normal from abnormal could be made using the Q amplitude alone.

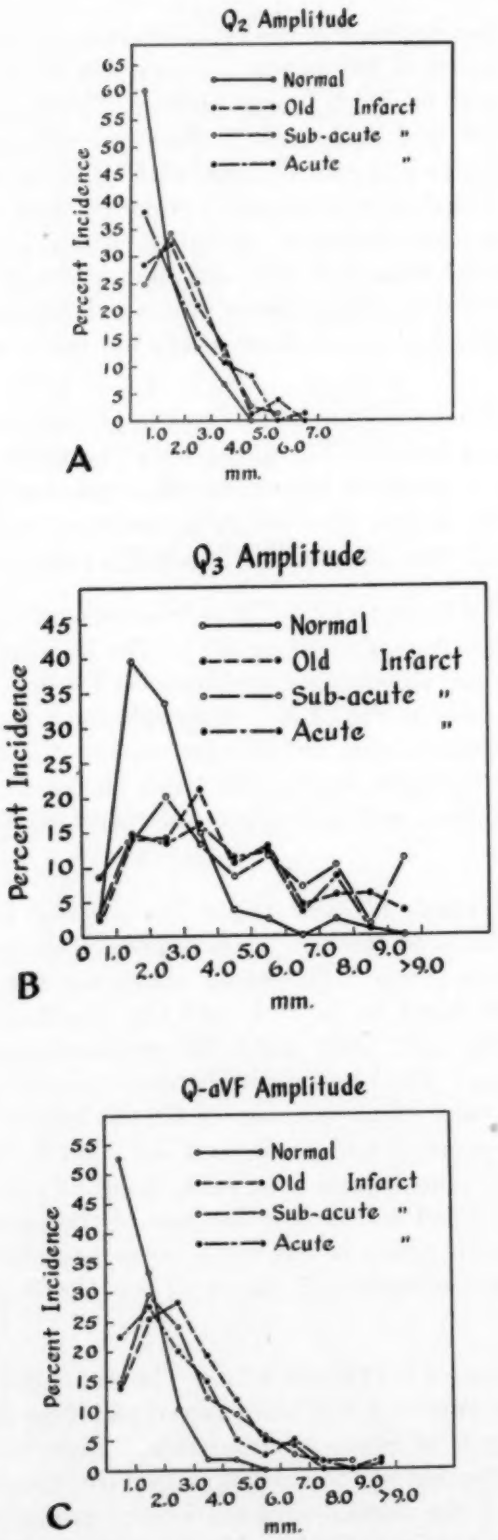


Fig. 3.—Frequency distribution (ordinate: incidence in per cent) in normal population, and in patients with posterior wall myocardial infarct (acute, subacute, old), of the Q_2 amplitude (*A*), of the Q_3 amplitude (*B*), and of the Q_{aVF} amplitude (*C*).

In Table II we have compared the distribution of Q amplitudes in our normal and old infarct groups with the combined normal group of Graybiel and associates[22] and Stewart and Manning.[21] It is interesting that the incidence of Q_2 was about the same in our preselected normal group as in the group of young aviators.

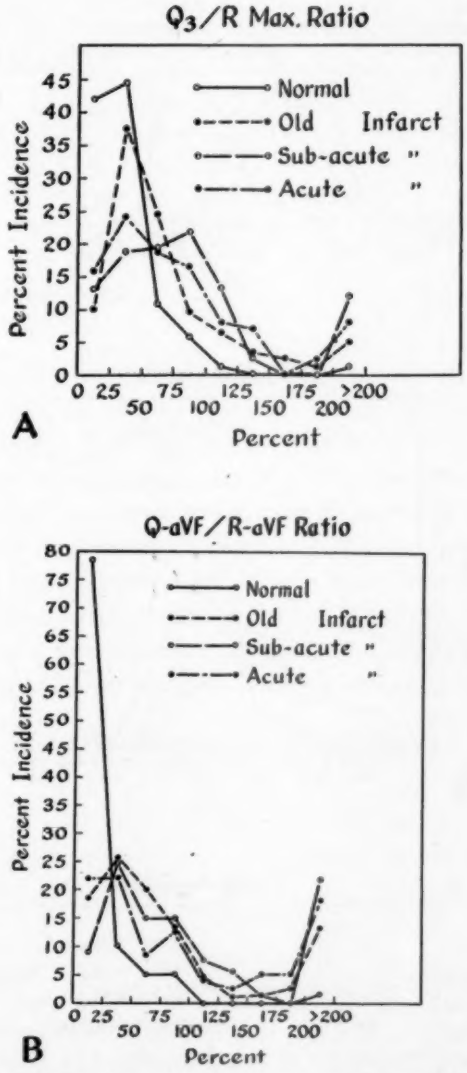


Fig. 4.—Frequency distribution (ordinate: incidence in per cent) in normal population, and in patients with posterior wall myocardial infarct (acute, subacute, old), of the Q_3/R maximum ratio (*A*), and of the Q/R ratio in aV_F (*B*).

Of the forty-two patients in whom serial tracings were present over a 6-month or longer period, two or almost 5 per cent subsequently lost the Q wave in Lead III without development of a subsequent anterior infarct.

Ratios—Q_3/R Maximum and Q_{aVF}/R_{aVF}.—Most electrocardiographers feel that a Q/R ratio is of greater significance than single amplitudes. We have therefore analyzed the most commonly used ratios—Q_3 amplitude: maximum R amplitude in the standard leads and the Q/R ratio in aV_F. The distribution curves (Fig. 4) are skewed and mean values therefore are statistically meaningless. The median values for the normal and old infarct groups are listed in

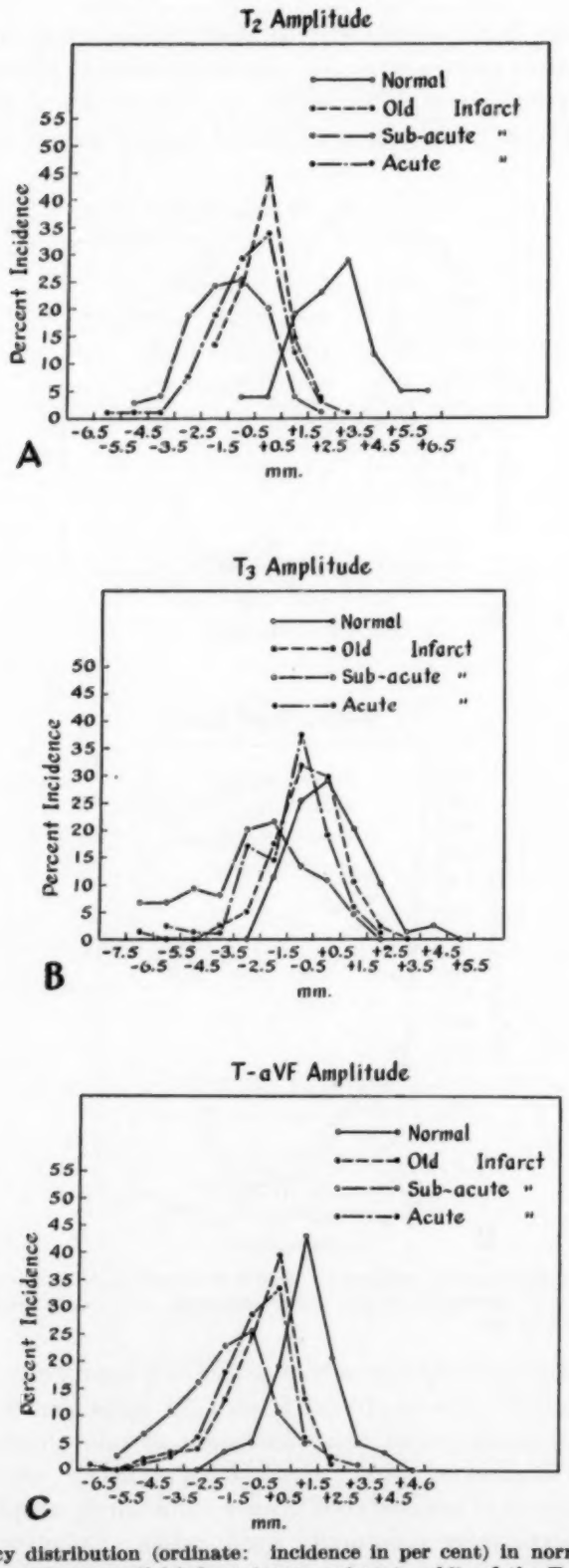


Fig. 5.—Frequency distribution (ordinate: incidence in per cent) in normal population, and in patients with posterior wall myocardial infarct (acute, subacute, old), of the T_2 amplitude (*A*), of the T_3 amplitude (*B*), and of the T_{aVF} amplitude (*C*).

Table III. It is apparent that even our median value for Q_3/R maximum in the normal group is higher than the generally accepted upper normal limit of 25 per cent. Although 90 per cent of the infarct tracings had a higher ratio than 25 per cent, this was true also for 59 per cent of the normal group.

TABLE II. DISTRIBUTION OF Q AMPLITUDES IN LEADS II, III, AND aV_F IN THE NORMAL GROUP AND IN THE GROUP OF OLD POSTERIOR WALL INFARCTS, AS COMPARED TO THE COMBINED NORMAL GROUPS OF STEWART AND MANNING[21] AND GRAYBIEL AND ASSOCIATES[22]

	PER CENT INCIDENCE OF PROMINENT Q			DISTRIBUTION RANGE OF Q (0.1 MV.)		
Group	Lead II	III	aV_F	II	III	aV_F
Normals	65	100	72	0–3.0	0.6–9.0	0–5.0
Old Infarcts	94	100	98	0–5.5	0.2–15.0	0–9.5
Normals (Stewart and Manning, Graybiel et al.)	64	65	—	0–4.0	0–6.0	—

The Q/R ratio in aV_F provides a somewhat better differentiation. Twenty per cent of the normal group and 81 per cent of the old infarct group had a ratio greater than 25 per cent. The median for the normal group was 17.8 per cent (Table III), as compared to 58.6 per cent in the patients. There is, however, still considerable overlap in the distribution of normals and patients. A relatively good differentiation between normals and posterior infarct patients with the Q/R ratio in aV_F was reported by Myers and Oren[9] and by Rubin and associates[12] but the overlap in the latter material was quite considerable, and this was true also in twelve autopsied cases of Fiske.[8] Therefore, the differentiation of normal from abnormal based on Q/R ratios is not reliable.

TABLE III. MEDIAN VALUES FOR RATIOS OF Q AND R AMPLITUDES

	Q_3/R MAX. (%)	Q/R IN aV_F (%)
Normals	28.6	17.8
Infarcts (old)	54.2	58.6

T Wave—Leads II, III and $_aV_F$.—Distribution curves for the normal and infarct groups in each lead are presented in Fig. 5. A significant difference between the normal and old infarct groups exists only for T_2 where a much higher proportion of the old infarcts have negative T waves. By current definition, T_2 should be positive in all normal individuals; however, there also were a small number of normal persons with negative T_2 in Graybiel's group of 1,000 young aviators. In our material, the inverted T_2 was found only in the group of hospital patients with normal myocardium at autopsy. In all leads, the amplitude of the negative T wave increases to a maximum in the subacute stage, which conforms to the evolution of a posterior wall infarct. The means, standard deviation, and percentage of positive T waves are listed in Table IV for our normal and old infarct group and compared to the normals from the combined series of Stewart and Graybiel and associates.[21,22] A highly significant

difference between the means for normals and old infarcts is present only in Lead II. Two subjects of our group with normal myocardium at autopsy had a Q_2 associated with negative T_2. In each instance old rheumatic valvular disease was present, although no microscopic evidence of myocardial injury existed.

TABLE IV. MEANS (M) AND STANDARD DEVIATION (S.D.) OF T AMPLITUDES (0.1 mv.) IN LEADS II, III, AND aV_F, AND INCIDENCE OF POSITIVE T WAVES IN THESE LEADS IN PER CENT, AS COMPARED TO THE COMBINED NORMAL GROUPS OF GRAYBIEL AND ASSOCIATES[22] AND STEWART AND MANNING[21]

	LEAD II		LEAD III		LEAD aV_F		INCIDENCE OF POSITIVE T		
	M.	S.D.	M.	S.D.	M.	S.D.	LEAD II	LEAD III	LEAD aV_F
Group									
Normals	1.96	1.5	0.007	1.4	0.98	1.1	96.2	45	88
Old Infarcts	−0.15	1.1	−0.90	1.6	−0.52	1.2	48.0	25	34
Normals (Graybiel et al., Stewart and Manning)	3.55	1.4	1.15	1.3	—	—	99.7	74	—

Evaluation of the Diagnostic Accuracy of Q_3 and Related Items in Terms of Frequency of Expected Diagnostic Errors.—Diagnostic errors in the use of any diagnostic criterion are derived from two sources: a false diagnosis of normal in patients and a false diagnosis of abnormal in normal persons. The ratio of the total number of false diagnoses to the number of correctly diagnosed patients is a valid expression of the diagnostic accuracy of any method.[5]

It can be seen from the overlapping distribution of normals and patients in the various items (Figs. 1 to 5) that no clear dividing line exists.

In all items, the extreme upper normal limit includes a large number of patients, and the extreme lower limit for patients includes a very large number of normals. The best discriminatory value, i.e., one with the minimum of diagnostic errors, will lie between these extremes.

In general, larger values will increase the number of diagnostically missed patients and decrease the number of false diagnoses in normals, while smaller values will decrease the number of missed patients, but will increase the number of false diagnoses in normal persons. This is illustrated in two examples (Q/R ratio in aV_F; Q_3 interval) in Table V.

It has been generally overlooked in the medical literature that the composition of the population group of which the patients are a part is important for the diagnostic accuracy of a method. We have arbitrarily chosen three population groups for analysis, all composed of individuals in their fifth and sixth decades: (A) a random male population, (B) hospital mixed population, and (C) hospital male population with an estimated 1, 5, and 10 per cent of patients with posterior infarct, respectively.

The composition of the hospital population was estimated from data obtained at this laboratory[23] in the spring of 1954. A statistical survey was made of the total number of patients hospitalized on the medical services of representative general hospitals in Minneapolis and St. Paul. Of over 500 patients

studied at any one time, approximately 10 to 12 per cent were considered by their ward physician to have history and ECG evidence of myocardial infarction. From the nearly even distribution of anterior and posterior infarct in 1,200 ECG's from the file of the Veterans Administration Hospital* with the diagnosis of infarct, it was further estimated that one-half of such patients (or 5 per cent of the total number) would have a posterior infarct.

TABLE V. NUMBER OF DIAGNOSTIC ERRORS (MISSED PATIENTS (MP), FALSE ABNORMAL (FA), AND ERROR RATIO (ER*) FOR VARIOUS DISCRIMINATING VALUES (D) OF THE Q/R RATIO IN aV_F AND OF THE Q_3 INTERVAL, IN (A) RANDOM MALE POPULATION: 990 NORMAL AND 10 PATIENTS WITH POSTERIOR WALL INFARCT; (B) HOSPITALIZED MEN AND WOMEN: 950 NONINFARCT AND 50 INFARCT; (C) HOSPITALIZED MEN: 900 NONINFARCT AND 100 INFARCT

ITEM	D	POPUL. A			POPUL. B			POPUL. C		
		MP	FA	ER*	MP	FA	ER*	MP	FA	ER*
Q/R_{aVF}	10%	0.1	154.4	15.6	0.5	148.2	3.0	1	140.4	1.4
	15%	0.7	112.9	12.2	3.5	108.3	2.4	7	102.6	1.2
	25%	1.9	39.6	5.1	9.5	38.0	1.2	19	36.0	0.68
	70%	6.3	13.9	5.4	31.5	13.3	2.4	63	12.6	2.0
Q_3 int.	.03	0.3	156.4	16.1	1.5	150.1	3.1	3	142.2	1.5
	.04	1.9	53.5	6.8	9.5	51.3	1.5	19	48.6	0.83
	.045	5.4	7.9	2.9	27.00	7.6	1.5	54	7.2	1.3

*The error ratio (ER) is the total number of diagnostic errors (false abnormal and missed patients) divided by the number of correctly diagnosed patients.

The survey in the Minneapolis hospitals included men and women. Limitation to male population is estimated to increase the number of patients with posterior infarct to 10 per cent. We are aware that the estimate of 1 per cent infarct patients in the random population (A) may be somewhat high, but is sufficient for an appraisal of the diagnostic accuracy in the first approximation.

Thus, in the populations A, B, C, each consisting of 1,000 individuals, 100, 50, and 10, respectively, will have posterior wall infarct and 900, 950, and 990, respectively, will have no infarct. In addition, we have to consider that 20 per cent of healthy males in their fifth and sixth decade have a prominent Q_3, as reported previously in this study.

Taking, as an example for the calculation, a Q_{aVF} interval of 0.04 sec. in population (A), 20 per cent or 180 of the 900 normals in this group will have prominent Q_3 and require differentiation from the patients with infarct.

According to our distribution, 7 per cent of the 180 normal subjects have values over 0.04 sec. and thirty-six patients have values below 0.04 sec. Therefore, 0.07×180 or 12.6 normals will be falsely classed as abnormal and 0.36×100 or 36 patients missed, totaling 48.6 false diagnoses. The number of infarcts correctly diagnosed in this population group will be $0.64 \times 100 = 64$. The ratio $48.6/64 = 0.75$, then represents the number of false diagnoses in patients and normals for each patient with a posterior infarct correctly diagnosed. Thus, in this example for every four patients correctly diagnosed, three false diagnoses will be made.

*We are indebted to Miss Mildred Shuler for this analysis.

For determination of the best discriminating value, the ratio of false to correct diagnoses was calculated for several values for each item. Two examples for this procedure are given in Table V (Q/R ratio in aV_F and Q_3 interval). Increase of the values (column 1) decreases the number of false abnormal diagnoses but increases the number of missed patients. The best discrimminating value (i.e., the lowest-error ratio) for the Q/R ratio in aV_F is 25 per cent. It was not possible to find a better ratio with graphic interpolation. For the Q_3 interval, 0.04 sec. is the best discriminating value for population group C, but 0.045 is the best value for population group A. This demonstrates that the diagnostic accuracy depends on the definition of the population group.

TABLE VI. NUMBER OF DIAGNOSTIC ERRORS [MISSED PATIENTS (MP), FALSE ABNORMAL (FA)], AND ERROR RATIO (ER*) IN THREE DIFFERENT POPULATIONS FROM 45 TO 60 YEARS (A, B, C, SAME AS IN TABLE V) FOR THE BEST DISCRIMINATING VALUES (D) IN SINGLE ITEMS

ITEM	D	POPUL. A			POPUL. B			POPUL. C		
		MP	FA	ER*	MP	FA	ER*	MP	FA	ER*
Intervals										
1. Q_{aVF}	.04	3.6	13.9	2.7	18.	13.3	0.98	36	12.6	0.75
2. Q_3 peak	.035	6.1	9.9	4.1	30.5	9.5	2.1	61	9.0	1.8
3. Q_{aVF}, peak	.03	6.0	4.0	2.5	30	3.8	1.7	60	3.6	1.6
4. R_3, peak	.06	4.0	11.9	2.6	20	11.4	1.0	40	10.8	0.84
5. R_{aVF}, peak	.055	6.2	5.9	3.2	31	5.7	1.9	62	5.4	1.7
Amplitudes										
6. Q_2 (mm.)	> .5	1.5	85.1	10.2	7.5	81.7	2.1	15	77.4	1.1
7. Q_3 (mm.)	>5.0	6.2	11.9	4.6	31	11.4	2.2	62	10.8	1.9
8. Q_{aVF}	>2.5	5.5	9.9	3.4	27.5	9.5	1.6	55	9.0	1.4
Ratios										
9. Q_3/R max.	(I-III) 25%	1.0	116.8	13.1	5	111.1	2.6	10	106.2	1.3

*The error ratio is the total number of diagnostic errors (false abnormal and missed patients) divided by the number of correctly diagnosed posterior wall infarcts.

Q_3 interval and Q/R ratio in aV_F are listed in Table V.

Tables VI and VII show the best discriminating values found for the various items, Table VI for single items and Table VII for several combinations. Many more combinations were evaluated, but only those with a relatively low-error ratio are shown. It is of interest that an inverted T_3 did not add to the diagnostic accuracy and, therefore, was not included in Table VII. On the whole somewhat better diagnostic ratios are obtained using single criteria derived from Lead aV_F rather than Lead III. The best (lowest) error ratios were found in the following four single items: for hospital population (C), the ratio of Q_{aVF}/R_{aVF}; Q_{aVF} interval; R_3 peak interval; and Q_3 interval (.04 sec.); and for random population (A), Q_{aVF} interval; R_3 peak interval; Q_3 interval (0.045 sec.); and Q_{aVF} interval.

The best criterion in our material is the ratio of Q_{aVF}/R_{aVF} of 25 per cent in population (C) but even with this item approximately 0.7 incorrect diagnoses will be made for each correct one.

TABLE VII. NUMBER OF DIAGNOSTIC ERRORS [MISSED PATIENTS (MP), FALSE ABNORMAL (FA)] AND ERROR RATIO (ER*) IN THREE DIFFERENT POPULATIONS (A, B, C, SAME AS IN TABLE V) FOR THE BEST DISCRIMINATING VALUES (D) IN COMBINATIONS OF ITEMS

TABLE VII. NUMBER OF DIAGNOSTIC ERRORS [MISSED PATIENTS (MP), FALSE ABNORMAL (FA)] AND ERROR RATIO (ER)* IN THREE DIFFERENT POPULATIONS (A, B, C, SAME AS IN TABLE V), FOR THE BEST DISCRIMINATING VALUES (D) IN COMBINATIONS OF ITEMS

ITEM COMBINATION	D	POPUL. A			POPUL. B			POPUL. C		
		MP	FA	ER	MP	FA	ER	MP	FA	ER
1. Q_3 interval Q_{aVF}/R_{aVF}	= or > .04 > 25%	3.5	14.8	2.8	17.5	14.2	.97	35	13.5	.75
2. Q_3 duration Q_{aVF} duration	= or > .04 = or > .04	9.1	9.9	2.3	20.5	9.5	1.0	41	9	.85
3. Q_3 duration Q_3/R max.	= or > .04 > 25%	2.5	43.6	6.1	12.5	41.8	1.4	25	39.6	.86
4. Q_{aVF} duration Q_{aVF}/R_{aVF}	= or > .04 > 25%	4.3	7.9	2.9	21.5	7.6	1.0	43	7.2	.88
5. Q_3 duration R_3 duration	= or > .04 = or > .06	4.4	9.9	2.5	22	9.5	1.1	44	9.0	.94
6. Q_{aVF} duration R_3 peak int.	= or > .04 = or > .06	5.1	5.0	2.1	25.5	4.8	1.2	51	4.5	1.10
7. R_3 peak int. Q_{aVF}/R_{aVF}	= or > .06 > 25%	5.2	2.0	1.5	26	1.9	1.2	52	1.8	1.1
8. R_3 peak int. Q_3/R	= or > .06 > 25%	4.9	7.9	2.5	24.5	7.6	1.3	49	7.2	1.1
9. Q_{aVF} duration Q_3 duration R_3 peak int.	= or > .04 = or > .04 = or > .06	5.4	5.0	2.3	27	4.8	1.4	54	4.5	1.3
10. R_3 peak int. Q_{aVF}/R_{aVF} Q_3/R max.	= or > .06 > 25% > 25%	5.7	2.0	1.8	28.5	1.9	1.4	57	1.8	1.4
11. Q_{aVF} int. R_3 peak int. Q_{aVF}/R_{aVF}	= or > .04 = or > .06 > 25%	5.9	2.0	1.8	29.5	1.9	1.5	59	1.8	1.5
12. Q_{aVF} peak int. R_3 peak int.	= 94 > .03 = or > .06	6.7	0	2.0	33.5	0	2.0	67	0	2.0

It is surprising that, in general, combination of items does not significantly improve the diagnostic accuracy for hospital population. However, this has previously been noted by Durant[24] in 1934, who actually found a deterioration of the diagnostic accuracy of Pardee's criterion by combination with additional items.

DISCUSSION

The best discriminating value for normal population, including 95 per cent or more, does not necessarily provide the best discrimination between normals and patients with infarct due to the considerable overlap of both groups. For instance, the critical value for the combination of the peak interval of Q_{aVF} (0.03 sec.) and R_3 (0.06 sec.), item 12 in Table VII, includes 100 per cent of the normal group, but misses 67 per cent of the patients. In the evaluation of the total errors of any diagnostic procedure, therefore, both normal and abnormal distribution must be considered, and this study may serve as an example of application.

The incidence of 23.2 per cent[28] and 18.6 per cent[29] of abnormal Q_3/R maximum ratios (25 per cent) in hospitalized patients without cardiac pathology compares reasonably well with the 12 per cent predicted for such population (Table V, columns) from the 106.2 false abnormals in 900 no-infarct patients (hospital population C).

Combination of various items did not improve the diagnostic accuracy for hospital population but for random population (A) many combinations (No. 2, 6, 7, 9, 10, 11, 12, as listed in Table VII) had a lower error ratio than the best single item, the Q_{aVF} peak interval with a ratio of 2.5.

Since the incidence of men with posterior infarct in random population is probably lower than our estimate of 1 per cent, the actual error ratios probably will exceed those listed in Table VII.

Even the best items, the ratio Q_{aVF}/R_{aVF} for hospital population (C) with an estimated 10 per cent posterior infarct cases, and the combination (No. 7) for random population, show rather poor discrimination, with 0.75 and 1.5 diagnostic errors, respectively, for each patient correctly diagnosed. This agrees quite well with the percentage of errors in the material of Levine and Phillips[34] and Wolff and associates[30] for the diagnosis of old myocardial infarct.

These authors found the incidence of correct diagnoses in acute infarct much higher, and also in our material the diagnosis was correct in all 18 autopsied cases. This might appear surprising, since the distribution of the various items is not very different in the acute, subacute, and chronic phase (Figs. 1 to 5). The higher incidence of correct diagnoses in acute infarct is due to the presence of S-T elevation, development of QRS changes, and evolution of the S-T and T changes.

In the subacute phase, the incidence of correct diagnoses will be higher due to changes of the T wave in serial ECG's, or their large amplitude in single ECG's.

Our results show that Q_3 and all related items such as listed in Tables VI and VII have a very limited value for the recognition of old posterior wall infarct,

and also for acute and subacute infarct unless serial ECG's are available. Since posterior wall infarct is the only lesion which is known to produce a prominent Q_3 in the majority of cases, it can be concluded that its diagnostic value for any other specific lesion must be still poorer, in fact approaching zero.

This, however, does not mean that a prominent Q_3 and related items are irrelevant. It is quite possible that a prominent Q_3 may indicate general myocardial involvement, although such involvement cannot be related safely to any specific lesion. It is known that the incidence of myocardial degeneration increases significantly with age even in the absence of corroborating clinical history, as shown in a large autopsy material.[14]

Experience in life insurance companies shows a correlation between mortality and a prominent Q_3.[31-33] From this point of view it is of interest that the incidence of a prominent Q_3 is much higher (20 per cent) in our normal group of 185 middle-aged men than in our group of 118 young men (12 per cent).

One of the interesting results of this study is the demonstration that the diagnostic value of any item depends on the composition of the normal population from which the patients have to be separated.

In general, the diagnostic accuracy decreases with the incidence of patients, but there are large differences between the various items in this respect. For instance, the ratio of Q/R amplitude in aV_F has the lowest error ratio for hospital population (C) with 10 per cent posterior infarct cases, but has one of the highest error ratios for random population. In general, the diagnostic error ratio for recognition of infarct will be smaller in a population with a higher percentage of coronary disease.

Orginally, this study was undertaken for the purpose of selecting the most representative initial instantaneous vector for spatial vector analysis. The Q wave in Leads II, III, and aV_F represents the initial part of the QRS loop in the frontal plane, directed upward and opposite to the main part of the loop.

The most representative instantaneous initial vector for normal population is the mean Q peak interval which is 0.022 and 0.018 sec., respectively, for Q_3 and Q_{aVF}. These values, however, discriminate poorly between normals and patients, which applies to vector analysis as well as to analysis of scalar ECG.

SUMMARY

The diagnostic significance of a prominent Q_3 and ten related electrocardiographic items was statistically evaluated from the distribution in a group of 90 normal subjects with a prominent Q_3 and 150 patients with posterior wall myocardial infarct. The evidence of a prominent Q wave in 170 normal men increased from 12 per cent in young men to 20 per cent in 250 older men. There was no significant difference in the distribution of most items in three different phases of infarct (acute, subacute, chronic).

The diagnostic accuracy was expressed as the ratio of diagnostic errors (false abnormal plus missed patients) to the number of correct diagnoses of infarct. The calculations were performed for three population groups: (A) random population of middle-aged men, with an estimated 1 per cent incidence of old infarct, (B) hospital mixed population with an estimated 5 per cent

incidence of old infarct, and (C) hospital male population with an estimated 10 per cent incidence of infarct. The estimates of the posterior wall infarct incidence in hospital populations is based on surveys in Minneapolis hospitals.

The calculations were made with different discriminating values, for the single ten ECG items as well as various combinations of items. Those values which were satisfactory for the normal group (i.e., the 95 to 98 per cent normal range limits) did not always give the lowest ratio of diagnostic errors. This demonstrates that both normal and abnormal distribution are necessary to determine the diagnostic accuracy of any method.

It was shown that the diagnostic accuracy of any item depends on the composition of the population group, within which the patients have to be diagnostically differentiated. In general, the diagnostic accuracy improves with the incidence of patients, it is lowest in the random population (A). The best diagnostic accuracy for single items was obtained in population (C) with a Q/R ratio of 25 per cent in aV_F, but even with this item for four correct diagnoses three diagnostic errors will be made. Combination of various items improved the diagnostic accuracy for random population, but not for hospital population.

SUMMARIO IN INTERLINGUA

Super le base del distribution de Q_3 e de 10 elementos electrocardiographic de character affin, observate in 90 individuos normal con prominentia de Q_3 e in 150 patientes con infarcimento myocardiac del pariete posterior in tres phases (i.e., acute, subacute, e chronic), le exactitude diagnostic de ille elementos esseva exprimite como le proportion de errores diagnostic (anormalitates false plus patientes non identificate) al numero de correcte diagnoses de infarcimento. Nos demonstrava le necessitate de information in re distributiones tanto normal como etiam anormal pro determinar le exactitude diagnostic que depende etiam del frequentia del morbo in le gruppo del population intra le qual le patientes debe esser differentiate diagnosticamente. Iste frequentia es minus in le population general que in le population de un hospital. Varie combinationes del elementos observate resultava in un melioration del exactitude diagnostic pro gruppos non seligite del population sed non pro le population de un hospital. Mesmo de melior elemento, exhibiente le plus alte discrimination (proportion Q/R de 25 pro cento in aV_F), non permitte plus que quatro diagnoses correcte pro cata tres errores diagnostic in le population de un hospital. Le frequentia de un prominente Q_3 cresce in le population normal con le etate del subjectos.

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STANDARDIZATION OF PHONOCARDIOGRAPHY

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ON THE recommendation of Dr. Kleyn, of The Hague, and Professor Lian, of Paris, two meetings were held, one in September, 1950, at *La Clinique Médicale de la Pitié*, during the First World Congress of Cardiology, and the other, also in Paris, on January 17, 1953, at the Technical Session of *La Société Française de Cardiologie.*

At this latter meeting, there were present, in addition to the two organizers, Dr. Maasz, of Bremen; Dr. Leatham, of London; Professor Lequime, of Brussels; Messrs. Bekkering and Mol, of Holland, and Georges Minot, of Paris, engineers Dean Giraud, of Montpellier; Professor Doumer, of Lille; Doctors Facquet and Milovanovitch, of Paris, and a goodly number of French cardiologists.

Among the foreign cardiologists who had been invited to this meeting but who were unable to attend were Professors Coelho, of Lisbon; Burger, of Bilthoven, Holland; Wolheim, of Wurzburg; Weber, of Bad Nauheim; and Mannheimer, of Stockholm; and Doctors Wood, of London; Duchosal, of Geneva; Holldack, of Heidelberg; Snellen, of Holland; Puddu, of Rome, and others.

Agreement was reached on the following points:

1. Phonocardiography is the graphic recording of cardiac sounds and murmurs. As a consequence, the sensitivity of phonocardiographs should be calculated on that of the human ear, represented by Fletcher's curve. The scale of vibrations would range from 15 to 800. In fact, the lower vibrations at 15 are not audible, and in order to render practical the construction of a phonocardiograph, it is recommended that the vibrations be not in excess of 800 per second. It is to be understood that the frequency of the vibrations recorded should be parallel to the cardiac vibrations. Thanks to the executive of the Dutch Poste, Telegráphe, Téléphoné, calibration of cardiographs may be carried out in a special laboratory.

2. To complete the phonocardiographic data thus gleaned, it is permissible to include in the recording certain vibratory frequencies with the object of obtaining better recording of audible phenomena and a more comprehensive analysis of the frequencies of the vibrations of which the cardiac sounds and murmurs are composed. With this in mind, the possibility of recording several tracings has been considered. For the present, it is thought wise to add only two tracings to the standard tracing which corresponds to the average sensibility of the ear.

Received for publication Dec. 20, 1954.

One of these two tracings would record the vibrations of low frequency; the other, those of high frequency. For this, it is necessary to introduce a filter for each type of recording. It is also necessary that the aggregate recorded by the phonocardiograph (microphone, amplifier, recorder) and the filter achieve the desired end.

3. The speed of the film shall be standardized at 5 or 10 cm. per second.

4. Finally, the legend for each tracing recorded should indicate if the apparatus used were designed for low or high frequencies. It was suggested by Dr. Duchosal that the following abbreviations be used to indicate the position of the microphone:

2 L 3 – Second left space 3 cm. from the left sternal rim
3 R 4 – Third right space 4 cm. from the right sternal rim
2 M – Mediosternal line at the height of the second space, etc. . . .

5. Lower frequencies at 15 per second should be eliminated. Otherwise, there is a risk of recording nonaudible vibratory groups, causing the clinician to err in his interpretation of the tracing. In any case, if the apparatus employed records lower frequencies at fifteen vibrations, this should be stated in the legend for the tracing, or the tracing could be called a vibrocardiogram rather than a phonocardiogram. In this way, the clinician would know that the vibratory groups recorded do not necessarily all correspond to the cardiac sounds and murmurs which he has noted by auscultation.

CONCLUSION

In the opinion of the previously named authors, these data might serve as a basis in arriving at a practical standardization of phonocardiography.

TEXTO IN INTERLINGUA

Al recommendation de Dr. Kleyn del Haga e Prof. Lian de Paris, duo conferentias habeva loco: le un in septembre 1950 durante le Prime Congresso Mundial de Cardiologia al *Clinique Médicale de la Pitié* a Paris; le altere, etiam a Paris, le 17 de januario 1953 al Session Technic del *Société Française de Cardiologie.*

Ultra le duo organisatores, le sequente personas assisteva al secunde de iste conferentias: Dr. Maaz de Bremen, Dr. Leatham de London, Prof. Lequime de Brussel, le ingenieros seniores Bekkering e Mol de Hollanda e Georges Minot de Paris, Decano Giraud de Montpellier, Prof. Doumer de Lille, Drs. Facquet e Milovanovitch de Paris, e un considerabile numero de cardiologos francese.

Le sequente personas esseva inter le extra-francese cardiologos qui habeva essite invitate sed qui non se trovava capace a assister a iste secunde conferentia: Profs. Coelho de Lisbona, Burger de Bilthoven in Hollanda, Wolheim de Würzburg, Weber de Bad Nauheim, e Mannheimer de Stockholm, e Drs. Wood de London, Duchosal de Geneva, Holldack de Heidelberg, Snellen de Hollanda, e Puddu de Roma.

Le conferentia se poneva de accordo in re le sequente punctos:

1. Phonocardiographia es le registration graphic de sonos e murmures cardiac. Per consequente le sensibilitate de phonocardiographos deberea esser calculate super le base del sensibilitate del aure human, representate per le curva de Fletcher. Le scala de vibrationes se extenderea ab 15 a 800 vibrationes per secunda. De facto, vibrationes inferior a 15 non es audibile. A fin de render le construction de phonocardiographos minus difficile in le practica, il es a recommendar que le vibrationes non excede 800 per secunda. Il debe esser presupponite que le frequentia del vibrationes registrate es parallel al vibrationes cardiac. Gratias al gerentia del hollandese P.T.T. (Posta, Telegrapho, e Telephono), le calibration de cardiographos pote esser executate in un laboratorio special.

2. Pro completar le datos phonocardiographic assi obtenite, il es permissibile includer in le registration certe frequentias vibratori que servi le objectivo de obtener melior registrationes de phenomenos audibile e un plus comprehensive analyse del frequentias de ille vibrationes que compone le sonos e murmures cardiac. Super le base de iste considerationes on ha pensate al possibilitate de registrar plure traciamentos. Al tempore presente on crede sage adder solo duo traciamentos al traciamento standard correspondente al sensibilitate median del aure. Un de iste traciamentos additional registrarea le vibrationes a basse frequentia, le altere le vibrationes a alte frequentia. Pro isto il es necessari introducer un filtro pro cata typo de registration. Il es etiam necessari que le aggregato registrate per le phonocardiographo (microphonio, amplificator, registrator) e le filtro attinge le objectivo desirate.

3. Le rapiditate del pellicula es a standardisar a 5 o 10 cm per secunda.

4. Finalmente, le legenda pro cata registration deberea indicar si le apparato usate esseva destinate a basse o alte frequentias. Dr. Duchosal proponeva que le sequente abbreviationes sia usate pro indicar le position del microphonio:

2 L 3—Secunde spatio sinistre, 3 cm ab le margine sinistrosternal;
3 R 4—Tertie spatio dextere, 4 cm ab le margine dexterosternal;
2 M—Linea mediosternal al altitude del secunde spatio, etc.

5. Frequentias inferior a 15 per secunda deberea esser eliminate. Alteremente on curre le risco de registrar nonaudibile gruppos vibratori, lo que pote resultar in errores del parte del clinico in su interpretation del traciamentos. In omne caso, si le apparato empleate registra frequentias inferior a 15 vibrationes, iste facto deberea esser indicate in le legenda del traciamento, o le traciamento deberea esser appellate un vibrocardiogramma plus tosto que un phonocardiogramma. Assi le clinico saperea que non omne le gruppos vibratori in le traciamento corresponde necessarimente al sonos e murmures cardiac que ille ha notate in le auscultation.

CONCLUSION

In le opinion del supra-nominate autores, iste datos pote servir como base pro un standardisation practic de phonocardiographia.

THE SPATIAL VECTORCARDIOGRAM IN CONGENITAL HEART DISEASE AND RIGHT VENTRICULAR HYPERTROPHY

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IN THE course of an investigation of spatial vectorcardiography, patients with cardiac and/or pulmonary disease known to result in right ventricular or combined ventricular hypertrophy were studied. The vectorcardiographic method used in this laboratory is described elsewhere.[1] These studies revealed definitive diagnostic features in right ventricular hypertrophy and clarified the mechanisms responsible for the electrocardiographic patterns in these cases.[2] The present paper deals with our findings in atrial septal defect, pulmonic stenosis, and tetralogy of Fallot (Table I).

MATERIAL

There were sixteen cases of atrial septal defect. Ten were uncomplicated and thus presumably had isolated right ventricular hypertrophy. However, one of the three patients in this group who came to surgery for correction of the defect died, and autopsy disclosed right and left ventricular hypertrophy, but the cause of the latter remained obscure. A complicating lesion was present in the other six cases, five of whom were studied by cardiac catheterization. The additional lesion was ventricular septal defect in one, pulmonary vascular obstructive disease in two, anomalous pulmonary venous drainage in two, and pulmonic stenosis in one.

There were twelve patients with pulmonic stenosis. This was the only lesion in six; two in this group were studied by cardiac catheterization and one by angiocardiography. In the six cases with lesions in addition to pulmonic stenosis, ventricular septal defect was present in three cases, patent ductus arteriosus in one, and probably atrial septal defect in two.

Fourteen patients had tetralogy of Fallot. Eight of these had already been operated on for the creation of a shunt at the time vectorcardiographic studies were done; roentgen examination at the time of the vectorcardiographic studies showed left ventricular enlargement in six of the eight operated cases.

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Received for publication Dec. 17, 1954.

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TABLE I

PATIENT	AGE	CLINICAL DIAGNOSIS	ECG DIAGNOSIS	X-RAY		C.C.	A.	O.
				RIGHT	LEFT			
D.K.*	8	ASD	RVH; ?LVH	+	±	+	−	+
G.S.	8	ASD	RBBB; RVH	+	O	+	−	+
G.C.	13	ASD	RBBB; RVH	+	O	+	−	+
M.G.	40	?ASD	RBBB	+	O	−	−	−
E.N.	58	?ASD	RBBB	+	O	−	−	−
D.D.	10	?ASD	RBBB; RVH	+	O	−	−	−
V.A.	7	?ASD	RBBB	+	O	−	−	−
C.K.	3	?ASD	RVH	+	O	−	−	−
A.P.	8	?ASD	RBBB; RVH	+	+	−	−	−
H.C.	3	ASD	RBBB	+	O	−	−	−
K.F.	2	?ASD?PS	RBBB	+	O	−	−	−
J.H.	11	ASD-APVD	RBBB; RVH	+	+	+	−	−
C.M.	10	ASD-APVD	RBBB	+	O	+	−	−
H.M.	4	ASD-PVO	RBBB; RVH LVH	+	?	+	−	−
S.L.	9	ASD-PVO	RVH	+	O	Unsat.	−	−
J.M.	9	ASD-VSD	RVH; LVH	+	+	+	−	−
T.S.	9	PS	RBBB; RVH	+	O	+	−	−
T.C.	11	PS	RVH	O	O	Unsuc.	+	−
G.F.	21	PS	RBBB	+	O	−	−	−
E.K.	3	PS	RVH	?	O	−	−	−
M.P.	12	?PS?ASD	RVH	+	?	−	−	−
J.T.	3	?PS?ToF	RVH	+	O	−	−	−
L.L.	1	?PS-ASD ?ToF	RVH	+	O	−	−	−
B.P.	13	?PS-ASD ?ToF	RBBB; RVH	+	O	+	−	−
M.L.	14	PS-VSD	RBBB	+	O	+	−	−
L.K.	7	PS-VSD	Normal	+	O	+	−	−
L.B.	7	PS-VSD ?ToF	RBBB; RVH LVH	+	+	−	−	−

TABLE I (CONTINUED)

PATIENT	AGE	CLINICAL DIAGNOSIS	ECG DIAGNOSIS	X-RAY		C.C.	A.	O.
				RIGHT	LEFT			
S.D.	4	PDA; ?PS	RVH; LVH	+	?	−	−	−
R.L.†	8	ToF	RVH	+	+	−	−	+
M.P.†	10	ToF	RVH	+	+	−	−	+
B.G.†	4	ToF	RVH	+	+	−	−	+
R.I.†	13	ToF	RVH	+	+	−	−	+
J.D.†	6	ToF	RBBB; RVH	+	+	−	−	+
D.M.†	6	ToF	RBBB; RVH	+	+	−	−	+
J.S.†	6	ToF	RVH	+	O	−	−	+
L.K.†	4	ToF	RVH	+	O	−	−	+
R.C.	8	ToF	RVH	+	+	−	+	−
A.M.	4	ToF-Pseudo-truncus	RVH	+	O	−	−	−
H.B.	4	ToF	RVH	+	O	−	−	−
S.C.	3	ToF	RVH	+	O	−	−	−
H. MacI	3	?ToF	RVH	?	O	−	−	−
R.S.	3	?ToF	?RVH	+	O	−	−	−

*Died; autopsied.

†Studies done postoperatively.

X-ray evidence of ventricular hypertrophy; C.C. = cardiac catheterization; A. = angiocardiography; O. = operation; ASD = atrial septal defect; PS = pulmonic stenosis; APVD = anomalous pulmonary venous drainage; PVO = pulmonary vascular obstruction; VSD = ventricular septal defect; ToF = tetralogy of Fallot; PDA = patent ductus arteriosus.

RESULTS

Atrial Septal Defect.—

A. *Uncomplicated:* The vectorcardiograms in eight of the ten cases of this group are similar. Most of the QRSsÊ loop occupies an inferior, slightly anterior, and slightly leftward position (Fig. 1). The initial QRS vectors are directed superiorly in seven cases, slightly anteriorly in eight, and slightly to the right in six and to the left in two (Table II). The subsequent QRS vectors retain a more or less anterior direction and are directed inferiorly and to the left followed by QRS vectors of the centripetal limit with less and less orientation to the left and inferiorly. The late QRS vectors point anteriorly, superiorly, and to the right becoming slightly posteriorly directed in two cases terminally before returning to the 0 point (point of origin). The whole or just the terminal part of the QRS loop is clockwisely inscribed in the horizontal and coronal (frontal) projections and counterclockwisely inscribed in the sagittal projection. The largest of the

late rightward, anterior, and superior vectors are one-half to one-fourth the magnitude of the largest leftward, anterior, and inferior vectors.

The QRS loop in one case of uncomplicated atrial septal defect was similar to those just described except that the frontal projection had a "figure-of-eight" contour, and the initial forces were directed inferiorly; the proximal portion of the QRS loop in the frontal plane was counterclockwisely inscribed.

TABLE II

PATIENT	INITIAL FORCES			TERMINAL FORCES			PATIENT	INITIAL FORCES			TERMINAL FORCES		
	V	S	T	V	S	T		V	S	T	V	S	T
D.K.	D	A	R	U	P	R	J.T.	U	A	R	U	A	R
G.S.	U	A	R	U	A	R	L.L.	U	A	L	UD	O	R
G.C.	U	A	R	U	AP	R	B.P.	D	A	R	U	A	R
M.G.	U	A	L	U	A	R	M.L.	U	A	R	U	O	R
E.N.	D	A	L	UDU	PA	R	L.K.	U	A	L	U	P	R
D.D.	U	A	R	U	A	R	L.B.	U	A	R	U	A	R
V.A.	U	A	R	U	A	R	S.D.	D	A	R	U	P	R
C.K.	U	A	R	U	A	R	R.L.	U	A	L	D	P	R
A.P.	U	A	R	U	P	R	M.P.	U	O	L	U	P	R
H.C.	D	A	R	U	A	R	B.G.	U	A	R	D	A	R
K.F.	U	A	R	U	P	R	R.I.	U	A	R	U	A	R
J.H.	U	A	R	U	A	R	J.D.	U	A	R	U	A	R
C.M.	U	A	R	U	A	R	D.M.	U	A	R	U	AP	R
H.M.	D	A	O	U	P	R	J.S.	U	A	R	U	A	R
S.L.	D	A	R	UD	P	R	L.K.	D	A	R	U	AP	R
J.M.	D	O	R	U	A	R	R.C.	U	A	R	U	A	R
T.S.	U	A	R	U	P	R	A.M.	U	A	R	U	AP	R
T.C.	U	A	R	U	PA	R	H.B.	U	A	L	O	AP	R
G.F.	U	A	R	D	A	R	S.C.	U	A	R	O	A	R
E.K.	U	A	R	U	O	R	H. Mac	D	A	R	U	P	R
M.P.	U	A	R	D	A	R	R.S.	U	A	R	U	P	R

V = Vertical; S = Sagittal; T = Transverse; D = Down; U = Up; A = Anterior; P = Posterior; R = Right; L = Left; O = No Deviation.

The remaining case in this group of uncomplicated atrial septal defect differed from the others in that the entire terminal portion of the QRSsÊ loop was oriented posteriorly, superiorly, and to the right; as in the preceding case the initial QRS vectors were directed inferiorly. Autopsy in this case disclosed atrial septal defect, right and left ventricular hypertrophy, and endocardial sclerosis of the septum.

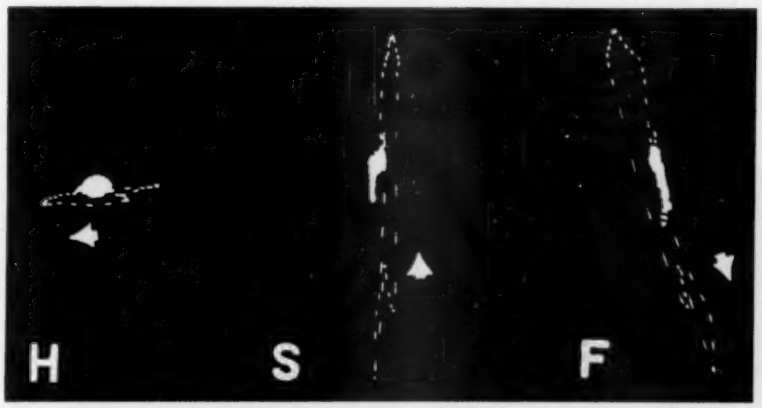

Fig. 1—Spatial vectorcardiogram of G.C. Atrial septal defect. The QRSsÊ loop is seen to be quite vertical. The initial QRS forces, obscured by the T loop in the horizontal projections, are seen to be directed superiorly, and only slightly anteriorly and to the right. The late QRS vectors, directed anteriorly, superiorly, and to the right, are about one-half to one-third the earlier peak leftward QRS forces.

Key to abbreviations for Figs. 1-9. H = horizontal projection; S = sagittal projection; F = frontal (or coronal) projection. The large and interrupted loop is the QRS projection for which the arrows indicate the direction of inscription. The heavy white loop is the T loop in each projection.

Fig. 2.—Spatial vectorcardiogram of J.H. Atrial septal defect and anomalous pulmonary venous drainage. The vectorcardiogram is similar to that of uncomplicated atrial septal defect (Fig. 1) except for the late rightward QRS forces which slightly exceed in magnitude the earlier leftward QRS forces.

The T loops in nine of the ten cases were oriented posteriorly, inferiorly, and to the left. The T loop in the autopsied case was oriented anteriorly, inferiorly, and to the left. In other words, the TsÊ loops in all the cases make an angle of 180° with the terminal QRS vectors. The T loops are clockwisely inscribed in the horizontal and coronal projections and counterclockwisely inscribed in the sagittal projection.

B. *Atrial septal defect complicated by pulmonary vascular lesions*:* The vectorcardiograms of these five cases are similar to those in the cases of uncomplicated atrial septal defect in respect to the position of the QRSsÊ loop, the direction of the initial and terminal QRS vectors (Table II), and the direction of inscription of the planar projections of the QRSsÊ loop. However, they differ in respect to the relative sizes of the peak leftward and late rightward QRS vectors. That is, the leftward vectors are relatively small and are equaled or exceeded by the late rightward QRS vectors. The T vectors are directed slightly anteriorly or posteriorly, and inferiorly and to the left; they are opposite to the terminal QRS vectors. The T loops in each projection have the same direction of inscription as the terminal part of the QRS loop (Fig. 2).

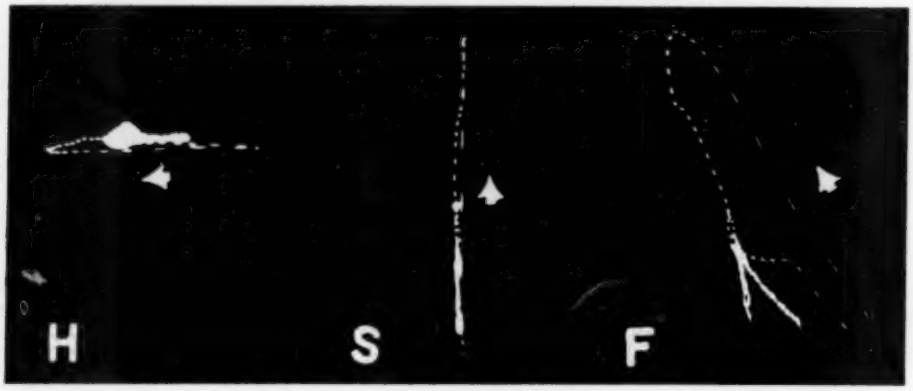

Fig. 3.—Spatial vectorcardiogram of J.M. Atrial and ventricular septal defects. The position of the QRSsÊ loop is difficult to define but appears to be vertical with the direction of the initial QRS forces consistent with such a position. Note however the counterclockwise inscription of F projection which suggests counterclockwise rotation consistent with left ventricular hypertrophy. The features of right ventricular hypertrophy are also present (see text).

C. *Atrial septal defect complicated by ventricular septal defect:* The QRSsÊ loop in this patient had an inferior, slightly anterior, and slightly leftward position (Fig. 3). The initial vectors had large projections to the right and anteriorly, and small projections superiorly. The subsequent QRS vectors of the centrifugal limb point inferiorly, slightly anteriorly, and to the left. The vectors of the centripetal limb, while pointing more to the left, have progressively smaller anterior and inferior projections. The leftward projection of the QRS vectors then decreases, and eventually the late QRS vectors are directed anteriorly, superiorly, then posteriorly, and to the right, before returning to the O point. This results in a "figure-of-eight" loop with counterclockwise inscription of the proximal loop and clockwise inscription of the distal loop of the horizontal and coronal projections; the sagittal loop projection is likewise "figure-of-eight" with the terminal part counterclockwisely inscribed. The T vectors are directed opposite to the terminal QRS vectors, and the T loops in each projection have the same direction of inscription as the terminal part of the QRS loop (Fig. 3).

***Anomalous pulmonary venous drainage, pulmonary vascular obstructive disease, or pulmonic stenosis.**

Pulmonic Stenosis.—

A. *Isolated and complicated by atrial septal defect:* The vectorcardiograms of six of the eight patients of this group (Fig. 4) were similar to those in the cases of atrial septal defect complicated by pulmonary vascular lesions (Fig. 2). The vectorcardiograms in the exceptional cases differed in two respects: The late rightward and anterior QRS vectors were inferiorly instead of superiorly directed, and the T loop was not separated from the terminal QRS vectors by 180° (Fig. 5). (These cases are described more fully in Section C under Tetralogy of Fallot.)

Fig. 4.—Spatial vectorcardiogram of J.T. Pulmonic stenosis. The QRSsÊ loop is similar to that of atrial septal defect complicated by anomalous pulmonary venous drainage (Fig. 2).

Fig. 5.—Spatial vectorcardiogram of M.P. Pulmonic stenosis with a question of additional atrial septal defect. The late QRS forces are directed inferiorly, anteriorly, and to the right, inconsistent with right bundle branch block.

B. *Pulmonic stenosis complicated by ventricular septal defect or by patent ductus arteriosus:* The vectorcardiogram in one of the three cases of pulmonic stenosis and ventricular septal defect was similar to those in uncomplicated atrial septal defect (Fig. 1). In the other two cases with these lesions (Fig. 6) and in the case of pulmonic stenosis with patent ductus arteriosus the QRSsÊ loop occupied an inferior, leftward, and slightly anterior position; the initial QRS vectors have large rightward and anterior and small superior or inferior projections; the subsequent QRS vectors of the centrifugal limb are directed

anteriorly, inferiorly, and to the left; the first QRS vectors of the centripetal limb are directed more to the left and less inferiorly and anteriorly, resulting in counterclockwise inscription of the early part of the frontal projection; the late QRS vectors are directed anteriorly, superiorly, and to the right, and the largest of these is smaller than the peak leftward QRS vectors; the terminal part of the QRS loop is clockwisely inscribed in the horizontal projection and counterclockwisely inscribed in the sagittal projection. The T loops are directed posteriorly, inferiorly, and to the left, 180° from the terminal QRS vectors; they are inscribed in the same direction as the terminal part of the QRS loop (Fig. 6).

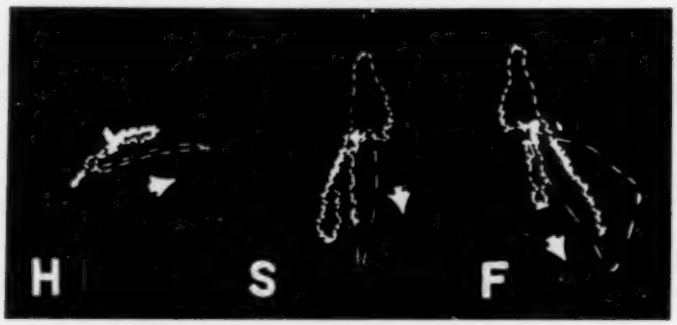

Fig. 6.—Spatial vectorcardiogram of M.L. Pulmonic stenosis with ventricular septal defect. This vectorcardiogram has all the features of right ventricular hypertrophy except for the presence of counterclockwise rotation, manifested by a "figure-of-eight" QRS loop in the frontal projection with the proximal portion counterclockwisely inscribed and initial QRS vectors having large rightward and anterior projections in the presence of a vertical loop (see text). The counterclockwise rotation is consistent with left ventricular hypertrophy.

Fig. 7.—Spatial vectorcardiogram of A.M. Tetralogy of Fallot with pseudotruncus (unoperated). The late rightward QRS vectors are four times the magnitude of the leftward QRS vectors.

Tetralogy of Fallot.—

A. *Unoperated cases:* The vectorcardiograms of four of the six cases in this group had the following characteristics (Fig. 7). The QRSsÊ loop as a whole is oriented anteriorly, to the right, and superiorly. The initial QRS

vectors point superiorly, slightly anteriorly, and slightly to the right or to the left. The subsequent QRS vectors are directed anteriorly, inferiorly, and to the left and are very small. They are followed by QRS vectors directed anteriorly, superiorly, and to the right. These attain a considerable magnitude and are approximately three to four times the magnitude of the earlier leftward QRS vectors. Terminally these vectors become somewhat posteriorly directed.

Fig. 8.—Spatial vectorcardiogram of D.M. Operated tetralogy of Fallot with postoperative left ventricular enlargement. The magnitudes of the leftward and late rightward QRS vectors are about equal.

Fig. 9.—Spatial vectorcardiogram of R.L. Operated tetralogy of Fallot with postoperative cardiac enlargement. Note the marked rightward projection of the late QRS vectors which, while not consistent with right bundle branch block because of their inferior direction, are distinctly abnormal.

The QRS loops are clockwisely inscribed in the horizontal and control projections and counterclockwisely inscribed in the sagittal projection. The T loops have the same directions of inscription as the QRS loops; they are directed anteriorly, inferiorly, and to the left, and are opposite to the terminal QRS vectors (Fig. 7).

The remaining two cases are described under Section C, which follows.

B. *Operated cases:* Two cases of this group had no x-ray evidence of postoperative left ventricular enlargement, and the vectorcardiograms were similar to those of the unoperated cases. Four of the six operated cases (Fig. 8)

which showed left ventricular enlargement had vectorcardiograms which were similar to those of uncomplicated atrial septal defect (Fig. 1). The remaining two postoperative cases are described in C which follows.

C. Six vectorcardiograms of the series of forty-two patients differed from the remaining ones. These included two cases of pulmonic stenosis, two cases of unoperated tetralogy of Fallot, and two cases of operated tetralogy of Fallot with postoperative left ventricular enlargement. These vectorcardiograms have the following features: the position of the QRSsÊ loop is anterior (in one case very extreme), inferior, and slightly to the left; the initial QRS vectors are directed anteriorly, superiorly, and to the right or to the left; the late and terminal QRS vectors are directed anteriorly, markedly to the right, and inferiorly at times forming bizarre gyrations; the horizontal and coronal QRS projections are terminally or wholly clockwisely inscribed; the sagittal QRS projection is wholly or terminally counterclockwisely inscribed; and the T vectors are directed somewhat posteriorly and to the left of the QRSsÊ loop (Figs. 5 and 9).

SUMMARY OF VECTORCARDIOGRAPHIC FINDINGS

Isolated Right Ventricular Hypertrophy.—The vectorcardiograms of this group are of two types. One has the following features: (1) the initial QRS vectors are directed superiorly or rarely inferiorly, slightly anteriorly, and slightly to the right or to the left; (2) the subsequent QRS vectors of the centrifugal limb are directed anteriorly, inferiorly, and to the left; (3) the early QRS vectors of the centripetal limb decrease in the leftward and inferior direction and are ultimately directed anteriorly or posteriorly, superiorly, and to the right; (4) the horizontal QRS projection is entirely or only in its terminal portion clockwisely inscribed; (5) the sagittal projection is, wholly or terminally, counterclockwisely inscribed; (6) the frontal projection is clockwisely inscribed in all cases but one; (7) the T vectors are directed inferiorly, to the left, and either slightly anteriorly, or slightly posteriorly; (8) the T loops are separated from the terminal QRS vectors by 180°; and (9) the T loops are clockwisely inscribed in the horizontal and coronal planes and counterclockwisely inscribed in the sagittal plane.

The other type seen in six cases is described as a group under tetralogy of Fallot, Section C.

Combined Right-and-left Ventricular Hypertrophy.—Five of the six vectorcardiograms in this group have the following features: (1) QRSsÊ loop lies inferiorly, slightly anteriorly, and to the left; (2) the initial QRS vectors are directed anteriorly, to the right, and slightly superiorly or inferiorly; (3) the subsequent QRS vectors of the centrifugal limb are directed anteriorly, inferiorly, and to the left; (4) the early QRS vectors of the centripetal limb point more to the left and less anteriorly and inferiorly than the preceding vectors; (5) the late QRS vectors are directed anteriorly or posteriorly, superiorly, and to the right; (6) the horizontal and coronal projections of the QRSsÊ loop are "figure-of-eight" with the proximal loop counterclockwisely inscribed and the distal loop clockwisely inscribed; (7) the sagittal projection of the QRSsÊ loop is "figure-of-eight" with the proximal loop clockwisely inscribed and the distal loop counterclockwisely inscribed; (8) the T vectors are directed inferiorly,

posteriorly, and to the left or opposite to the terminal QRS vectors; and (9) the T loops are clockwisely inscribed in the horizontal and coronal projections, and counterclockwisely inscribed in the sagittal projection.

DISCUSSION

The effects of heart position and rotation on the normal and abnormal spatial vectorcardiogram have been investigated by a simple and direct technique.[4] The vectorcardiograms of the patients with congenital heart disease and right ventricular hypertrophy have been analyzed with these experiments in mind. In isolated right ventricular hypertrophy which includes cases of atrial septal defect and pulmonic stenosis the position of the QRSsÊ loop is vertical with slight anterior displacement. In the unoperated cases of tetralogy of Fallot, the QRSsÊ loop differs in that it is anterior, superior, and to the right. Although the QRSsÊ loops in the two groups of cases point in opposite directions in the vertical axis, the initial vectors in both are identical. This means, according to the studies previously referred to, that the heart position is the same in both groups.

The terminal vectors in the cases of pulmonic stenosis, atrial septal defect complicated by pulmonary vascular lesions, and unoperated tetralogy of Fallot, point in some cases superiorly and posteriorly. The posterior deviation of these vectors is the result of marked anterior displacement of the loop.[5]

Fowler and associates[6] observed that there is a statistically significant tendency for the initial vectors in right ventricular hypertrophy to be directed to the left, due, they believe, to abnormal septal depolarization from right to left. However, our studies have revealed that clockwise rotation around the longitudinal axis of a vertical heart adequately explains the orientation of the initial vectors.

The effect of left ventricular hypertrophy on the vectorcardiogram is seen in the case of atrial septal defect combined with ventricular septal defect, the one with unexplained left ventricular hypertrophy, and four of the five cases of pulmonic stenosis complicated by ventricular septal defect or patent ductus arteriosus. The initial vectors in these cases are directed superiorly, and markedly anteriorly and to the right, an orientation which is characteristic of counterclockwise rotation around the longitudinal axis of a vertical heart. Rotation in this direction is also indicated by the counterclockwise inscription of the frontal projection of the QRS loop.[5]

It is evident that the vectorcardiograms in isolated right ventricular hypertrophy are both similar and different from those in combined ventricular hypertrophy. In both there is vertical heart position and moderate to marked anterior displacement of the apex. In right ventricular hypertrophy, there is moderate to marked clockwise rotation about the longitudinal axis of the heart, while in combined hypertrophy there is counterclockwise rotation.

As important as heart position and rotation are, alone they do not explain all the features observed in the vectorcardiograms of patients with right ventricular hypertrophy. Intrinsic factors, namely intraventricular block and increased right ventricular potentials, exert important influences. In uncompli-

cated right bundle branch block, the right ventricular potentials dominate the electric field late in the depolarization interval; consequently, the terminal QRS forces have an anterior, superior, and rightward orientation.[2,3,7,8] The terminal forces in thirty of our thirty-six cases of isolated right ventricular hypertrophy displayed these characteristics, and delayed depolarization of the right ventricle was therefore assumed to exist in these. However, important differences in the QRSsÊ loop of right bundle branch block with and without right ventricular hypertrophy occur.

In uncomplicated right bundle branch block the part of the QRS loop composed of the late QRS vectors is counterclockwisely inscribed in the horizontal projection and clockwisely inscribed in the sagittal projection. In the cases of right ventricular hypertrophy, however, the late portion of the QRS loop is inscribed clockwisely in the horizontal, and counterclockwisely in the sagittal projections. These differences cannot be explained on the basis of the conduction defect, or heart position and rotation, either alone or in combination.[5]

The instant at which right ventricular forces begin to exert an influence and the interval during which they dominate the electric field will depend on the degree of conduction delay in the right bundle branch, and on the relative strengths of the right and left ventricular forces. The beginning of right ventricular dominance can be recognized by a tendency toward anterior, superior, and rightward displacement of the QRS vectors. Since this deviation occurs earlier in the QRS interval in cases of right ventricular hypertrophy, than in cases of uncomplicated right bundle branch block of comparable degree, the conclusion is warranted that the earlier deviation is a manifestation of increased right ventricular potentials. These increased potentials, then, are responsible for the change in direction of inscription of the QRS loop (Fig. 10).

The mechanisms, therefore, responsible for the electrical patterns of most cases of isolated right and combined ventricular hypertrophy are: (1) Vertical heart position, anterior displacement of the cardiac apex, and clockwise rotation of the heart in isolated right ventricular hypertrophy, (2) vertical heart position, anterior displacement of the cardiac apex, and counterclockwise rotation of the heart in combined ventricular hypertrophy, (3) delay of right ventricular depolarization, and (4) increased right ventricular potentials. There is considerable difference of opinion concerning the role of these various mechanisms.[3,7,10]

In uncomplicated atrial septal defect, the leftward and inferior QRS vectors are two to four times the magnitude of the late rightward and superior QRS vectors. In atrial septal defect complicated by pulmonary vascular lesions and in uncomplicated pulmonic stenosis, the leftward and rightward QRS vectors are more or less equal in magnitude. In unoperated tetralogy of Fallot the late rightward QRS vectors are three to four times the magnitude of the earlier leftward QRS vectors.

Variations in degree of delay of right ventricular depolarization cannot account for these quantitative differences. The instant at which right ventricular forces appear is probably the same in most cases, while the effect they have on the vectorcardiogram depends on their magnitude, the right ventricular forces being greatest in uncomplicated tetralogy of Fallot, and least in uncomplicated atrial septal defect (Fig. 10).

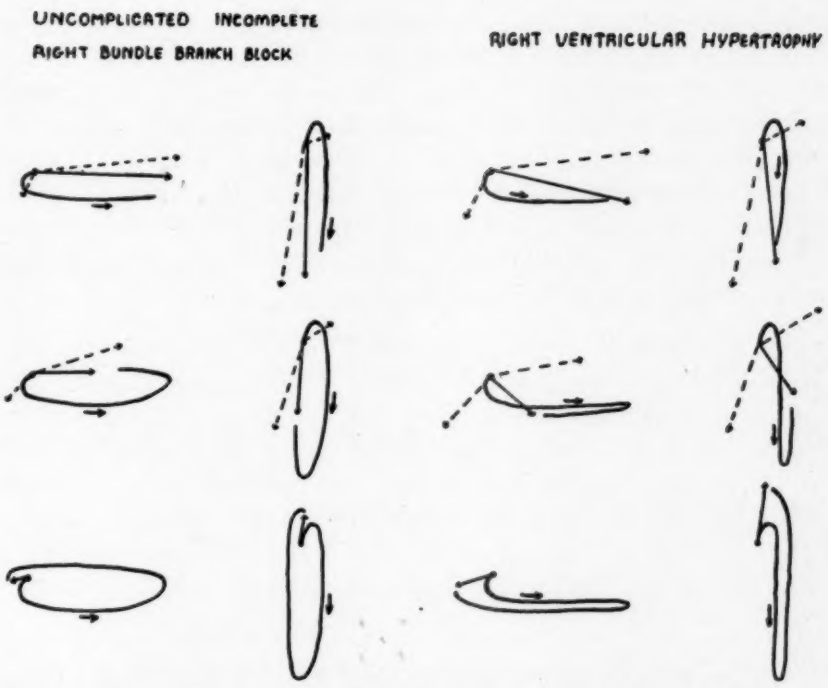

Fig. 10—Schematic representation of three comparable stages of ventricular depolarization in the vectorcardiograms of uncomplicated incomplete right bundle branch block and of right ventricular hypertrophy with right bundle branch block. Under the heading of each condition are represented three stages of the QRSsÊ loop. (The horizontal projection is on the left and the sagittal on the right in each stage.)

Uncomplicated Incomplete Right Bundle Branch Block.—The first stage (top) shows the QRS partially inscribed and arbitrarily represents a point shortly after the introduction of right ventricular forces. The broken arrows schematically represent vectors contributed by the left ventricle (large broken arrow directed posteriorly, inferiorly, and to the left) and the right ventricle (small broken arrow directed anteriorly, superiorly, and to the right). The resultant vector (solid arrow) is directed inferiorly and to the left.

The second stage (middle set) represents a period later in systole in which the left ventricular component is still larger than the right ventricular component and thus still dominates the magnitude and direction of the resultant vector (solid arrow) which is still to the left and inferior and slightly posterior, but the left ventricular component is beginning to wane and the right ventricular component is increasing slightly.

The third stage (bottom) represents a period in which left ventricular forces have been extinguished and the right ventricular forces dominate such that the resultant vector is directed anteriorly, superiorly, and to the right.

Right Ventricular Hypertrophy (With Right Bundle Branch Block).—The vectors in this set were derived from those of the figures of uncomplicated incomplete right bundle branch block except that the right ventricular component vectors were doubled in magnitude (length). At each of the three stages this one change is seen to cause the resultant vectors to be directed less to the left, posteriorly and inferiorly, or more to the right, anteriorly and superiorly, once right ventricular forces have been introduced. This change in the direction of the instantaneous cardiac vectors results in a change in direction of inscriptions of the horizontal and sagittal projections such that the former is clockwisely and the latter counterclockwisely inscribed, whereas in uncomplicated incomplete right bundle branch block the directions of inscription are the opposite.

Yet it is not the magnitude of the right ventricular forces alone which determines the direction and size of the resultant vectors from instant to instant. The relation between the right and left portions of the QRS loop depends upon the balance between the component ventricular forces. Thus it is the combination of increased right ventricular forces and diminished forces of the hypoplastic left ventricle in unoperated tetralogy of Fallot which is responsible for the 1:4 ratio between the left and right peak forces in four of six cases. Following the creation of a shunt, the left ventricle hypertrophies as in six of the eight operated cases, and the ratio between the peak right and left forces changes correspondingly as in four of the six cases. Therefore, the relationship between the leftward and rightward QRS vectors is not diagnostic of a specific lesion but is a reflection of right ventricular preponderance.

Six cases in the series of forty-two patients had vectorcardiograms which did not fulfill all the criteria described previously. These six cases included two with a diagnosis of pulmonic stenosis and four cases of tetralogy of Fallot, two unoperated and two operated. The QRSsÊ loops of these vectorcardiograms differed from the others only in that the late QRS vectors did not have the superior direction which is seen in right bundle branch block. It is therefore assumed that conduction delay plays no role in the vectorcardiographic pattern of these six cases referred to as the "intrinsic pattern."

The T vectors and loops in all the cases of this series, except those with the intrinsic pattern, have the same relation to the terminal QRS vectors as in uncomplicated right bundle branch block.[2] These observations are at variance with those of Lasser and associates,[10] who believe that the TsÊ loop is opposite the QRSsÊ loop as a whole.

In the intrinsic pattern the T vectors and TsÊ loops have a spatial position similar to the normal.

SUMMARY

1. Forty-two cases known to have congenital heart disease and right ventricular hypertrophy were studied by spatial vectorcardiograms.

2. Characteristic and diagnostic vectorcardiographic patterns are observed in right ventricular hypertrophy.

3. The mechanisms responsible for the vectorcardiographic patterns of most cases of right ventricular hypertrophy isolated or combined are (1) Position and rotation of the heart; (2) delayed right ventricular depolarization; and (3) increased right ventricular potentials.

4. In six cases of isolated right ventricular hypertrophy the mechanisms responsible for the vectorcardiographic pattern are (1) position and rotation of the heart, and (2) increased right ventricular potentials. This pattern is referred to as the intrinsic right ventricular hypertrophy pattern.

SUMMARIO IN INTERLINGUA

1. Esseva studiate per medio de vectocardiogrammas spatial quaranta-duo casos confirmate de congenite morbo cardiac e hypertrophia dexteroventricular.

2. Distincte configurationes de importo diagnostic es observabile in vectocardiogrammas de hypertrophia dextero-ventricular.

3. Le mechanismos responsabile pro le distincte configurationes vectocardiographic del majoritate del casos de hypertrophia dexteroventricular isolate o combinate esseva (1) le position e rotation del corde, (2) retardate depolarisation dexteroventricular, e (3) augmentate potentiales dexteroventricular.

4. In 6 casos de isolate hypertrophia dexteroventricular le mechanismos responsabile pro le configuration vectocardiographic esseva (1) position e rotation del corde e (2) augmentate potentiales dexteroventricular.

Le configuration es designate como le configuration intrinsec de hypertrophia dexteroventricular.

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THE CLOT DENSITY DETERMINATION OF FIBRINOGEN IN RHEUMATIC FEVER

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IN A previous study[1] we reported the results of serial determinations of the fibrinogen concentration and the erythrocyte sedimentation rate (ESR) in some pediatric conditions including a limited number of patients with rheumatic fever. The purpose of this report which is confined to patients with rheumatic fever is to evaluate the significance of the fibrinogen concentration as determined by the rapid clot density method elaborated by two of us (S.L. and B.W.V.)[2] and its response to cortisone therapy as well as its variations during and after the "rebound" following cessation of cortisone. Furthermore, a comparison between the respective fibrinogen concentration, the ESR and the C-reactive protein (CRP) values,[3,4] was attempted.

While most inflammatory processes lead to an elevation of the fibrinogen concentration[2,5-10] the magnitude of the response largely depends upon the affected organ as well as the extent of the lesion. It has been noted by us previously that upper respiratory and genitourinary infections produce only a moderate rise of the fibrinogen concentration, while, on the other hand, the presence of a definite and active rheumatic process is usually associated with a considerable and protracted rise of the fibrinogen concentration.[1]

It is well known that the ESR is predominantly affected by the plasma fibrinogen concentration,[11,12] while other factors are of less importance.[13-19] A complete parallelism of the ESR and the fibrinogen concentration in rheumatic fever as well as in other conditions could be expected only if it also existed between the latter and all globulins. It has been shown, however, that some globulins, such as gamma globulin[20] remain persistently elevated following an exacerbation of rheumatic activity. This may explain the fact that the ESR is found to be elevated for prolonged periods subsequent to an attack of rheumatic fever, and long after the fibrinogen concentration has returned to normal. It seemed, therefore, of considerable importance to study serially the one factor which is of foremost significance in the determination of the ESR, namely, the fibrinogen concentration.

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Received for publication Nov. 6, 1954.

MATERIAL

This study includes thirty-nine patients in various phases of rheumatic fever. They were divided into four groups. Group 1 consists of twenty-one patients with a monocyclic type of acute rheumatic fever and carditis. Group 2 includes three cases with a polycyclic type of rheumatic fever and carditis. Group 3 comprises nine children recovering from a recent bout of acute rheumatic fever. In Group 4 are six patients with known rheumatic heart disease who were studied but found to be inactive.

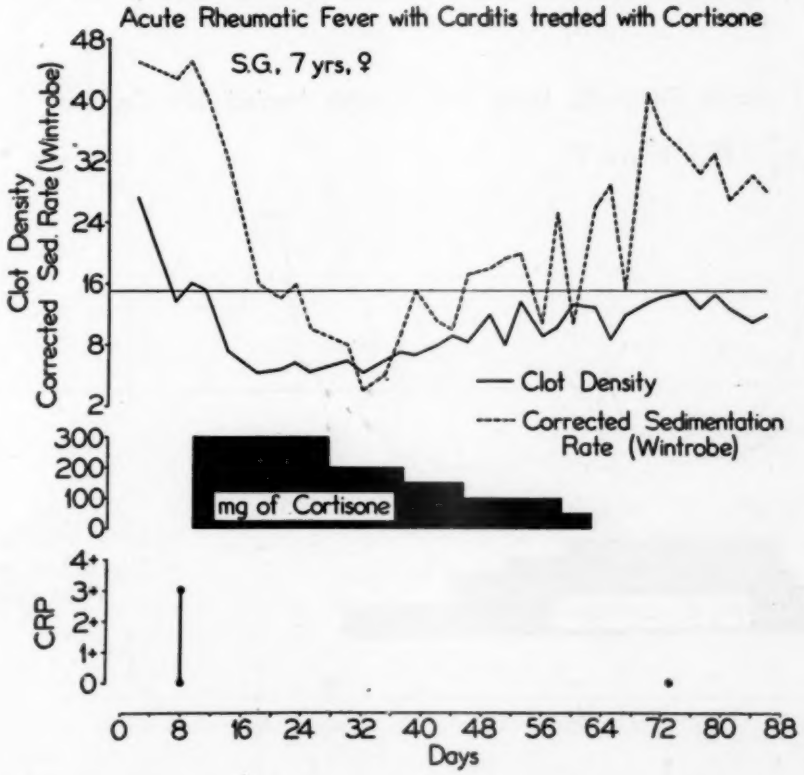

Fig. 1.—Erytyhrocte sedimentation rate, clot density, and C-reactive protein in a patient with monocyclic type of rheumatic fever. Fibrinogen is obtained in milligrams per 100 c.c.; from formula F = 18d + 120. (F = fibrinogen; d = clot density.)

METHODS

The ESR was determined serially by the method of Wintrobe and Landsberg.[21,22] Simultaneous determinations of the fibrinogen concentration were performed by the clot density method,[2] wherein the fibrinogen, F = 18d (clot density) + 120 in milligram per cent. Normal values of the clot density varied from 5 to 15 corresponding to a normal range of the fibrinogen concentration of 210 to 390 mg. per cent. The test for CRP was performed by the capillary precipitation method according to Anderson and McCarty.[4]

CASE REPORTS

Group 1.—The course of events in twenty-one patients with a clearly delineated episode of acute rheumatic fever and carditis which may be described as of the "monocyclic" type is well represented by the following three case histories.

CASE 1.—S.G., a 7-year-old girl was admitted with fever, joint pains and an evanescent rash over the lower extremities, three weeks following an upper respiratory infection. A harsh systolic murmur was audible over the entire precordium. On the tenth hospital day she was placed on cortisone for 7½ weeks. The "rebound" which occurred thereafter was characterized by a high normal fibrinogen level and a markedly elevated ESR still present at the time of discharge (Fig. 1.)

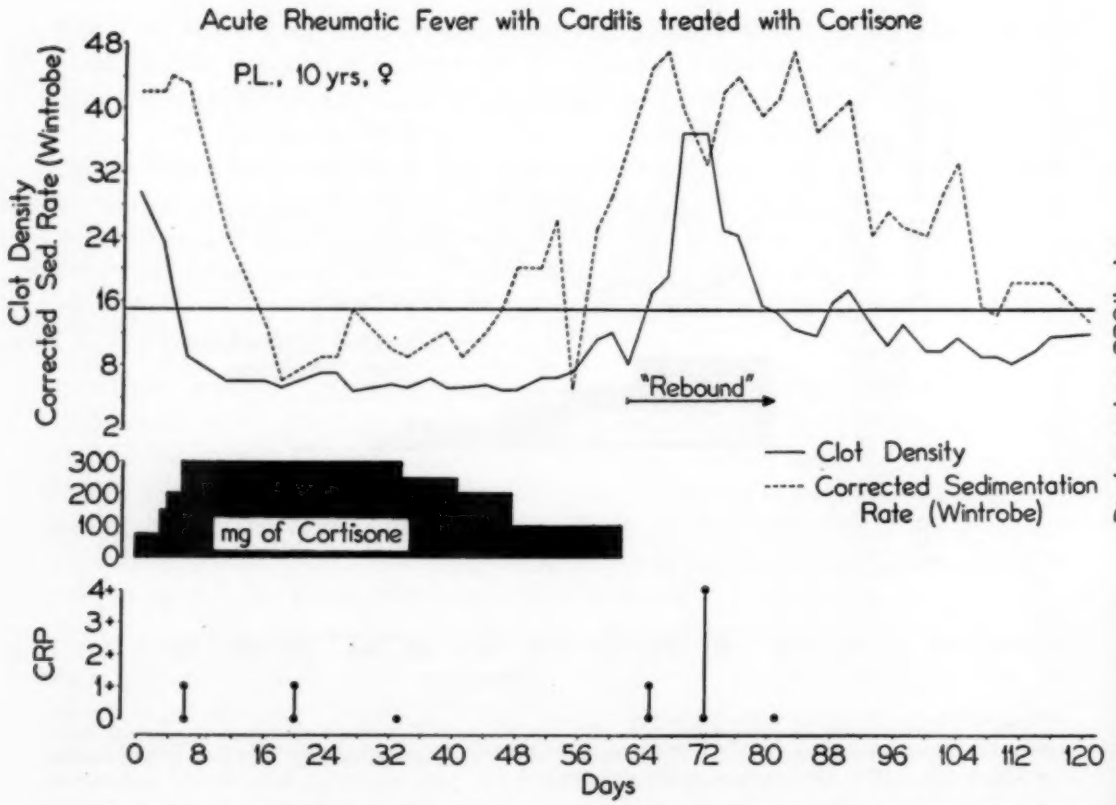

Fig. 2.—Erythrocyte sedimentation rate, clot density, and C-reactive protein in a monocyclic type of rheumatic fever with a pronounced "rebound" after cessation of cortisone. Fibrinogen is obtained in milligrams per 100 c.c.; from formula F = 18d + 120. (F = fibrinogen; d = clot density.)

CASE 2.—P.L., a 10-year-old girl was admitted 2½ months after a "virus infection" and 2 years after her first bout of rheumatic fever. On admission, a systolic murmur and a mid-diastolic rumble were heard at the apex as well as an early diastolic decrescendo murmur over the aorta. Blood pressure was 160/80 mm. Hg. P-R interval measured 0.02 second with a tachycardia of 125. There was an anemia of 10.4 grams hemoglobin, and 3.7 millions red blood cells. The child was placed on cortisone which was administered for the following 9 weeks. Cessation of cortisone led to a marked "rebound" with arthralgia, fever, and tachycardia as well as a resurgence of laboratory manifestations (Fig. 2).

CASE 3.—L.O., a 17-year-old boy, who had suffered three bouts of rheumatic fever since the age of 11, developed while on our wards a mild fever and transient T-wave changes in most precordial leads indicative of a carditic process. Treated with bedrest and penicillin, he displayed a moderate, transient rise of the fibrinogen level just following the appearance of ECG changes. The ESR, however, remained high throughout his hospital stay (Fig. 3).

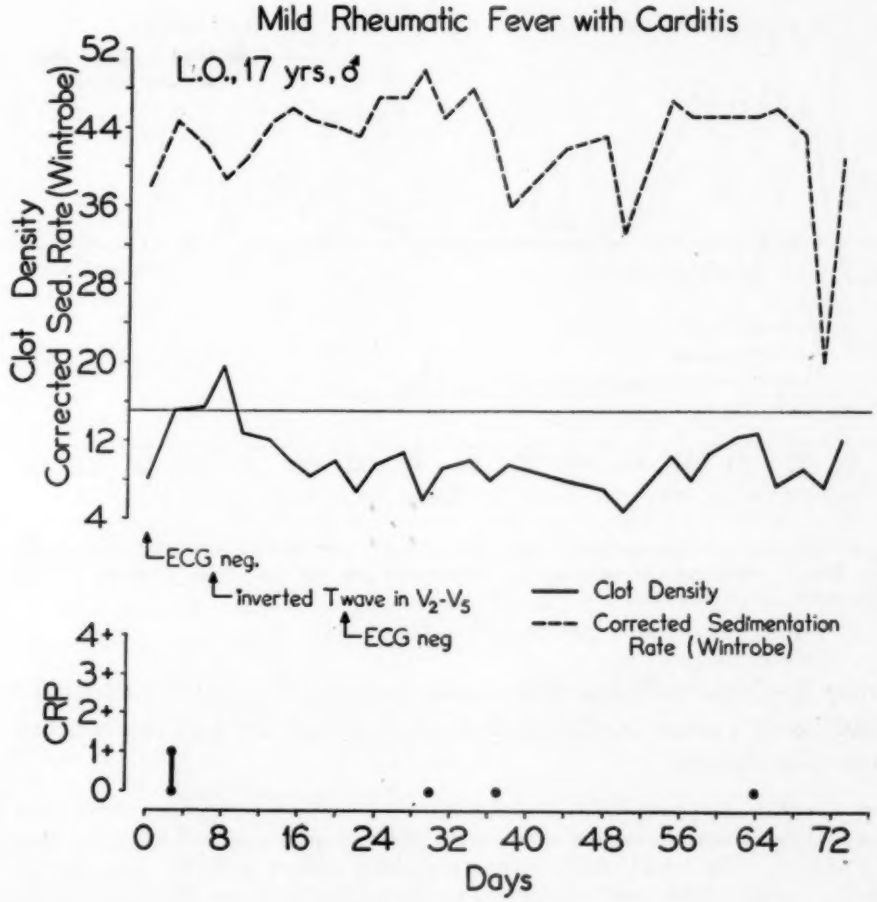

Fig. 3.—Erythrocyte sedimentation rate, clot density, C-reactive protein and ECG changes in a mild case of rheumatic fever. Fibrinogen is obtained in milligrams per 100 c.c.; from formula F = 18d + 120. (F = fibrinogen; d = clot density.)

Group 2.—The three patients in this group with a polycyclic type of rheumatic fever and carditis, in whom signs of activity did not recede but fluctuated intermittently, are well represented by the following case.

CASE 4.—M.J., a 10-year-old boy, was admitted after having suffered three bouts of rheumatic fever with carditis treated with steroids. During the 8½ months' stay at our institution he displayed five episodes of rheumatic exacerbation, mostly characterized by fever, joint pains, and electrocardiographic changes. The first five months of his hospitalization were characterized by marked fluctuations of the ESR during the acute phases as well as in the intervals between

exacerbations while the fibrinogen level more rapidly returned to normal values during the symptom-free intervals (Fig. 4). The first bout of rheumatic exacerbation proved electrocardiographically to be a pericarditis. The fibrinogen levels closely followed the electrocardiographic changes while the ESR continued to fluctuate at high levels.

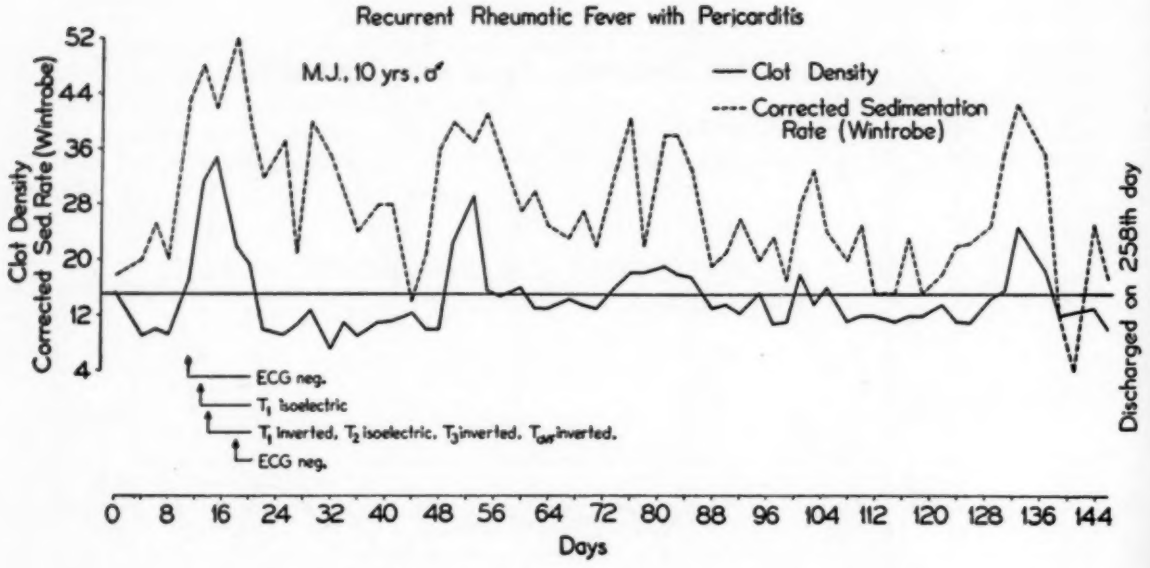

Fig. 4.—Erythrocyte sedimentation rate, clot density, and ECG changes in a polycyclic type of rheumatic fever. Fibrinogen is obtained in milligrams per 100 c.c.; from formula F = 18d + 120. (F = fibrinogen; d = clot density.)

Group 3.—Nine patients, each having sustained a frank attack of rheumatic fever and carditis prior to admission to our hospital, are well represented by the following case history.

CASE 5.—H.B., a 12-year-old boy with a history of recurrent rheumatic fever since the age of 6, was admitted three weeks after an exacerbation with arthralgia and fever for which he was treated at home. The initial febrile course responded well to penicillin and bedrest. While the ESR fluctuated at high levels during the entire hospital stay, the fibrinogen level remained normal except for a single determination two days after the CRP was 1+. Further observation failed to disclose signs of rheumatic activity (Fig. 5).

Group 4.—Six patients with a history of rheumatic fever suspected of having an acute exacerbation and admitted for diagnostic evaluation are represented by the following case.

CASE 6.—W.S., a 9-year-old boy with a history of recurrent rheumatic fever since the age of 2, was admitted with a high fever, tachycardia, cough, and chest pain. Clinical observation failed to substantiate a presumptive diagnosis of a rheumatic exacerbation. The ESR disclosed intermittent elevations, while the fibrinogen level remained normal throughout his entire hospital stay (Fig. 6).

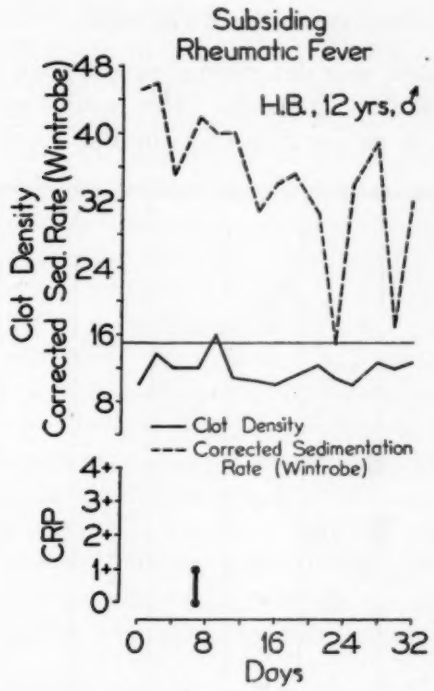

Fig. 5.—Erythrocyte sedimentation rate, clot density, and C-reactive protein in a patient with subsiding rheumatic fever. Fibrinogen is obtained in milligrams per 100 c.c.; from formula F = 18d + 120. (F = fibrinogen; d = clot density.)

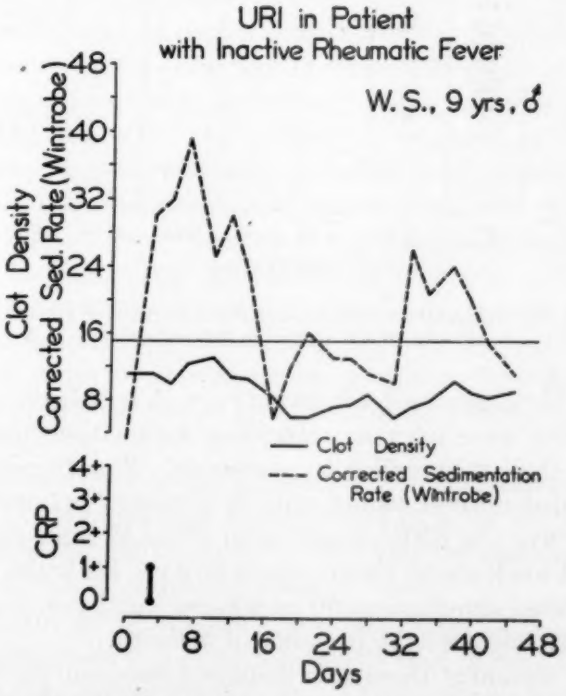

Fig. 6.—Erythrocyte sedimentation rate, clot density, and C-reactive protein in a known rheumatic patient with an upper respiratory infection. Fibrinogen is obtained in milligrams per 100 c.c.; from formula F = 18d + 120. (F = fibrinogen; d = clot density.)

C-REACTIVE PROTEIN

The C-reactive protein was determined seventy-six times and at least once in each patient reported in this series. The results were plotted against the corresponding clot density values obtained simultaneously (Fig. 7).

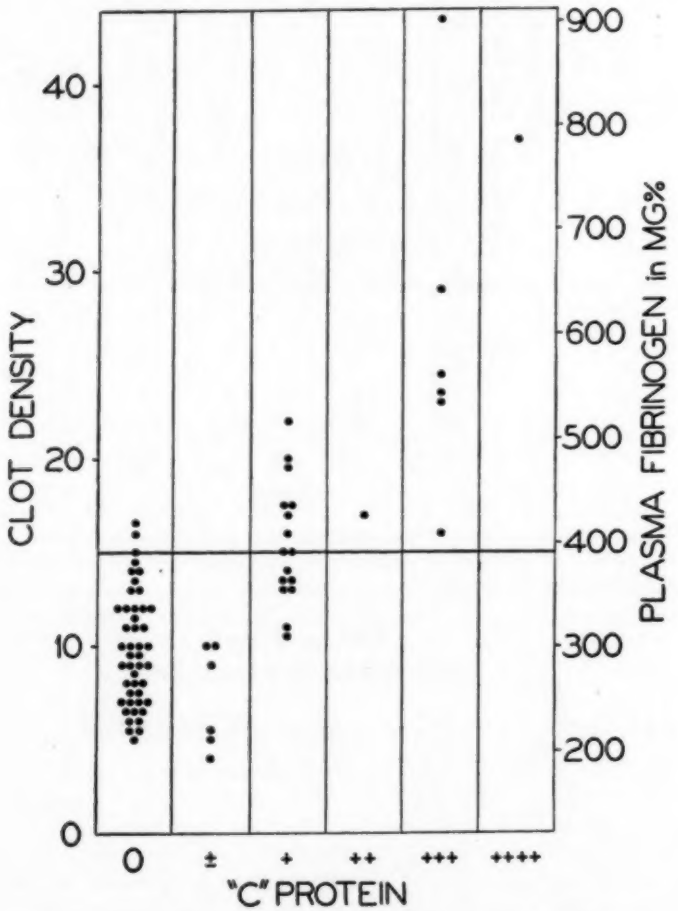

Fig. 7.—Comparison of clot density and C-reactive protein in seventy-six simultaneous determinations.

Results.—In forty-four out of seventy-six determinations both the CRP and the clot density were normal, coinciding with either absence of rheumatic manifestations or their suppression by cortisone. Simultaneous determinations of the ESR revealed normal values only in nineteen instances whereas in the remaining twenty-five the ESR ranged from 20 to 50 mm. per hour despite the absence of clinical evidence of rheumatic activity. Both the CRP and the clot density were elevated simultaneously in sixteen instances, and each time these elevations correctly mirrored the presence of activity.

In seventeen instances there was disparity between the CRP and the clot density. On two occasions a negative CRP was associated with a very mild elevation of the clot density. One of these two instances occurred at the end of a "rebound" following a course of cortisone. The second dissociated result was

encountered during the subsiding phase of a rheumatic exacerbation in another polycyclic case. In both these instances the CRP disappeared somewhat before the decline of the fibrinogen concentration, but the difference in time did not exceed 48 hours. On six occasions a ± CRP was associated with a normal clot density. In two of these, the patients were under treatment with cortisone; in three others the fibrinogen level reached normal values while a "rebound" was in the phase of subsidence and once such dissociation occurred in a polycyclic case during subsiding activity. On nine occasions a 1+ CRP was associated with a normal clot density. In four of these, the patients were recovering from a "rebound," and the CRP remained positive for a little longer than the elevation of the fibrinogen concentration. One patient had sustained an episode of pulmonary congestion due to mitral stenosis while on two occasions patients with a polycyclic form of rheumatic fever were recovering from an exacerbation. In another case, which showed transient electrocardiographic signs of carditis, the CRP was 1+ when the clot density was still at the upper limit of normal, but the latter value rose rapidly (L.O., Fig. 3). The ECG changes in this case coincided with the peak of the clot density values. The ninth instance was encountered in a patient who had sustained repeated episodes of rheumatic activity but who during this observation was suffering from an upper respiratory infection (W.S., Fig. 6).

DISCUSSION

The results of the serial fibrinogen determination by the clot density method in thirty-nine patients in various stages of acute rheumatic fever indicate that the values parallel the severity of the clinical condition. Patients with pronounced clinical manifestations and a protracted course showed a characteristically sustained high fibrinogen level while others with a more benign picture displayed a lower fibrinogen concentration and a tendency of these values to recede spontaneously. The decline of the clot density before institution of cortisone therapy was found in a total of fourteen of the twenty-one patients with a monocyclic form of acute rheumatic fever. In each of these fourteen individuals the clinical course proved to be benign and was followed by a very mild "rebound" after cortisone was discontinued. Although it may be questioned whether this trend was sufficient to warrant withholding of steroid therapy, it seemed to us that subsequent developments may have justified administering only moderate doses in these cases. The ESR, because of its indiscriminate elevation in all cases, was of no value for prognosis.

On the other hand, in seven patients the clot density continued to rise during hospitalization and exhibited persistently high levels. The clinical course in these patients was protracted and the "rebound" in each instance was severe, both clinically and from a laboratory point of view.

With the institution of cortisone the clot density always decreased and usually returned to normal values within two to four days. The ESR, however, lagged behind for about eight more days. This conforms with observations by others.[23,24] In one of the severest and most protracted cases, the ESR returned to normal about 40 days after the clot density, while in another severe case it

remained constantly elevated until discharge. Both were among the patients in whom the clot density had failed to display any tendency to a spontaneous decline before the institution of cortisone.

The response to cortisone was characterized not only by a decline of the clot density, but the values were often distinctly below those usually encountered in healthy children. Although it has been claimed[25,26] that ACTH exerts a nonspecific effect upon the fibrinogen level, our attempts to reproduce such depressant action in normal children by administering cortisone have been rather inconclusive.[1]

We found that in those patients who received 300 mg. of cortisone daily there was a close approximation of both the clot density and the ESR values, while in patients who were treated with 200 mg. daily the ESR either failed to approach normal levels or did so only after a very protracted course. On the other hand, two patients with a mild rheumatic process who were not treated with cortisone and two other patients who received only 200 mg. of cortisone daily also showed concurrent normalization of the clot density and ESR values. Such early approximation of the results of both tests clearly denoted the mildness of the rheumatic process while their divergence during cortisone therapy was more indicative of a rather severe clinical course.

Following cessation of cortisone therapy a "rebound" occurred in nine out of twenty-one patients with a monocyclic type of rheumatic fever which was characterized by a recurrence of arthralgia, fever, tachycardia, and laboratory findings such as an increased ESR, clot density, and reappearance of CRP.[27] The ESR was usually first to rise and was followed within 24 to 48 hours by an increased clot density and a reappearance of the CRP. Both the ESR and the clot density reached a plateau from which the clot density was always first to descend, reaching normal values within a few days, while the ESR continued to fluctuate at high levels for prolonged periods ranging from one to six weeks. During this phase, while the patient's condition both clinically and along laboratory lines was abnormal, we found the clot density to be the earliest and most reliable indicator of a recession in the inflammatory process. Whenever the clot density began to decrease, it presaged an improvement in the clinical picture and in the laboratory findings as well. Quite frequently, the CRP still remained slightly positive when the clot density had reached normal values and disappeared subsequently. The early descent of the clot density from the plateau reached after cessation of cortisone therapy identified this phase as a "rebound" rather than an exacerbation.

The three patients with a polycyclic type of rheumatic fever exhibited a clinical course which was most accurately reflected by the serial changes in the clot density values. In all instances, increasing manifestations of rheumatic activity were associated with an increase in the fibrinogen concentration. It seemed relevant that upper respiratory infections were accompanied by moderate elevations in the fibrinogen level, whereas episodes due to rheumatic exacerbations caused more frequently a significant rise in the clot density. Although the ESR rose 24 hours or so earlier than the fibrinogen level whenever an exacerbation occurred, it lagged behind the clot density by many days or even weeks when

the remission began. While no inference can be drawn as to a possible subsidence of the rheumatic process during the interval when the clot density is normal, it seems, nevertheless, quite significant that the normalization of the ECG coincides with the normalization of the fibrinogen concentration. Similarly, it has been pointed out previously[1] that the subsidence of a first degree A-V block may be accompanied by a decline of the fibrinogen values. From these data the conclusion seems to be justified that the fibrinogen concentration, while not specifically indicating the nature of the rheumatic process, reflects the magnitude of the inflammatory response to the rheumatic insult.

The nine patients included in Group 4 and having sustained a bout of frank rheumatic activity before admission to our institution failed to disclose elevated fibrinogen concentrations throughout a prolonged observation period. The normal clot density in these cases was in keeping with the absence of other signs of rheumatic activity, and none of these patients, therefore, received additional courses of hormone therapy. Ultimately, the ESR also returned to normal in many instances, but in others remained elevated after discharge, when the patients were followed in the outpatient department.

Similarly, intercurrent infections, such as those of the upper respiratory tract in patients known to have sustained previously an attack of rheumatic fever and carditis, did not alter materially the normal fibrinogen level. Any elevation of the clot density in such patients (Group 4) was found to be only moderate and very transient. The ESR, on the other hand, disclosed values undistinguishable from those encountered in patients with severe rheumatic fever.

The CRP, first reported by Tillet and Francis,[3] has been known to be present not only in pneumococcal pneumonia but also in a variety of other conditions such as rheumatic fever, staphylococcal osteomyelitis, subacute bacterial endocarditis, bacillary infections of the colon-typhoid group, and in noninfectious diseases such as carcinomatosis or myocardial infarction. In spite of the admitted lack of specificity for rheumatic fever the semiquantitative estimation of this serum protein can be considered a measure of the activity of the disease process.[4,26-28]

The results in our series of 76 determinations strongly suggest a parallelism between the CRP and the fibrinogen concentration. This is of particular interest because fibrinogen as a protein is not present in serum but in plasma only while the CRP is a serum constituent. The rheumatic insult seems to produce, therefore, alterations of elements of the protein spectrum which are rather distant from each other. The results of this study indicate that a close correlation exists between the two proteins and the clinical course. Some discrepancies between the CRP and the fibrinogen concentration were encountered in patients recovering from rheumatic fever in whom the fibrinogen concentration tended to decline at an earlier date than did the CRP. This, on the other hand, seemed to be of some prognostic significance inasmuch as the earlier decline of the fibrinogen concentration presaged a disappearance of the CRP and subsequently of the rheumatic process as well. It is, however, to be emphasized that the decline of the fibrinogen concentration in a patient with rheumatic fever does not constitute a sign of

absent rheumatic activity but only indicates that one protein fraction intimately associated with an inflammatory process is subsiding, thus disclosing a tendency of such inflammation to a remission. It has also been pointed out previously[1] that the suppression of hyperfibrinogenemia during the administration of cortisone is in no way attributable to absence of the rheumatic process. This also holds true for the suppression of the C-reactive protein during cortisone therapy which cannot be taken as indicating termination of the rheumatic process.[28]

CONCLUSIONS AND SUMMARY

After the diagnosis of acute rheumatic fever is established on clinical grounds the serial estimation of the fibrinogen concentration by the clot density method offers an auxiliary criterion in the evaluation of the clinical course. The severity of a case is indicated by a persistently high fibrinogen concentration whereas a mild course is suggested by a spontaneous decline to normal values before institution of cortisone therapy.

The adequate therapeutic effect of cortisone is reflected by a rapid normalization of the fibrinogen which seems to be the first blood constituent whose decline indicates a favorable response to treatment.

After cessation of cortisone therapy the "rebound" is characterized by a variable rise of the fibrinogen level which in most instances is in accordance with the severity of the rheumatic process.

The decline of the fibrinogen level from the peak reached during the "rebound" is the first laboratory indication of a subsidence of symptoms preceding the disappearance of the CRP as well as the decline of the ESR.

The values of the C-reactive protein were closely paralleled by those of the fibrinogen concentration. Dissociation of the values occurred in the presence of upper respiratory infections as well as during a "rebound."

SUMMARIO IN INTERLINGUA

Esseva usate le methodo del determination del densitate del coagulos fibrinogenic, vidite como un expression del magnitude del processo inflammatori, in le studio de 39 patientes con febre rheumatic in varie phases de activitate. Determinationes serial del tempore de sedimentation, del nivello de fibrinogeno (manifeste in le densitate del coagulo), e del proteina reactive a C esseva executate a frequente intervallos e pointe in correlation con le curso clinic.

Un persistente elevation del fibrinogeno plasmatic esseva constatate in casos sever, durante que un rapide reduction del densitate del coagulo ante le initiation de cortisona esseva associate con un leve processo rheumatic. Fibrinogeno pare esser le prime constituente del sanguine que descende al norma sub le effecto de cortisona. Post le "resurgentia" (que seque le cessation de cortisona) le declino de fibrinogeno es le prime indice de melioration clinic e laboratorial. Le correlation del valores de proteina reactive a C e de fibrinogeno revelava con pauc exceptiones un nette parallelismo.

We are indebted to the Mildred Forman Foundation for their contribution to the maintenance of the rheumatic fever patients. We wish to acknowledge the helpful cooperation of Dr. Ernest T. Heffer and Dr. Irving G. Kroop.

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VENA CAVA INFERIOR LIGATION IN CONGESTIVE HEART FAILURE

Report on 100 Cases in Five Years

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SINCE 1949, one of us (H. de B.) has taken a special interest in the treatment of congestive heart failure by ligation of the inferior vena cava. A large number of patients have been operated on at the Centre de Broussais, and the results of the first fifty cases were given in a paper read at the First World Congress of Cardiology held in Paris in September, 1950.

During the last four years our experience has widened considerably thanks to the regular "follow-up" observation of these first fifty cases and to the operations performed in the interval. We wish to present the complete statistics pertaining to our first hundred cases. They were operated on between April, 1949, and November, 1953, thus affording a lapse of one to five years for our observations. We have not taken into consideration the most recent cases because we think that the observation time has not been sufficiently long.

We shall not take up here the physiopathology of the ligation of the inferior vena cava in congestive heart failure or the various technical points involved in the operations, as they have already been dealt with in various publications, and we have no new contribution on the subject. On the other hand the object of the present report will be to study factors concerning indications, method of treatment, and results.

INDICATIONS

Almost all the forms assumed by heart failure (either right, left, or complete) are amenable to a caval ligation at some stage in their evolution. Because, however, of the specialization of our Medical Center, our indications apply for the most part to mitral heart diseases. If we consider on the one hand the type of heart failure and on the other the type of cardiopathy, Table I summarizes the distribution of our indications.

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Presented at the Second World Congress of Cardiology, Washington, D. C., September, 1954.

Received for publication Nov. 22, 1954.

TABLE I. DISTRIBUTION OF 100 PATIENTS OPERATED ON FOR LIGATION OF THE VENA CAVA, ACCORDING TO TYPE OF CARDIOPATHY AND TYPE OF CARDIAC FAILURE OPERATIVE INDICATIONS AND CLINICAL DIAGNOSIS

	TOTAL HF.	RVF EMBOLUS	RVF APE	RVF OTHERS	LVF	TOTAL
Stenosis	6	1	6			13
Mitral disease	17	9	6	2	1	35
Mitro-aortic disease	16	3	9	2	1	31
Arterial hypertension	5				8	13
Congenital cardiopathy	4					4
Without valvular lesion	3			1		4
Total	51	13	21	5	10	100

Total HF. = total number of men and women. RVF embolus = right ventricular failure with embolus. RVFAPE = right ventricular failure with acute pulmonary edema. RVF others = right ventricular failure with other conditions. LVF = left ventricular failure.

COMMENTS

First Category: Complete Cardiac Insufficiency.—In fifty-one cases the indications for surgery were serious congestive heart failure, with dyspnea of decubitus, hepatomegaly, and edema. The general condition of patients belonging to this class was very precarious because medical treatment (complete rest, digitalization, liquid restrictions, mercurial diuretics) brought no appreciable improvement. In fact, their condition was so poor that many of them (about 15) died between the day when the decision to operate was made and the day when the operation was to have been performed. These cases do not, of course, appear in our statistics.

A prolonged cardiopathy has always been a very unfavorable factor. At the very outset, its presence proved to coincide with very poor results following the caval ligation, most likely because of the irreversible and progressive damage to the subject's myocardium.

Among the fifty-one patients showing complete heart failure, eight had a pure stenosis, seventeen a mitral disease, and sixteen mitral and aortic disease. For five others, hypertension was the cause of cardiac insufficiency; four patients with congenital heart disease also received surgical treatment; two were afflicted with Ebstein's disease (a 10-year-old girl in the terminal phase and a 37-year-old man) and two with Lutembacher's disease. Finally, three patients had myocardial insufficiency without valvular lesions.

Second Category: Mitral Cardiopathy With Right Ventricular Insufficiency and Repeated Emboli.—In this category of thirteen cases, we grouped mitral cases showing more or less accentuated signs of right ventricular insufficiency and repeated pulmonary emboli.

Third Category: Mitral Cardiopathy With Predominating Pulmonary Side Effects.—To this third category of twenty-one patients belong mitral cases who had repeated attacks of acute pulmonary edema with more or less backflow into the right heart. Good results were obtained from the ligation of the in-

ferior vena cava before the advent of mitral commissurotomy. Since then, this form of surgery has become the rule in such cases and supersedes the ligation method.

Fourth Category: Right Ventricular Failure of a Particular Type.—This fourth category of five cases includes five patients showing signs of right ventricular insufficiency of average intensity: two of them are in a period of evolution (Observation 21 and 82), the third one presents a marked tricuspid lesion in addition to the mitral lesion. Hepatic disturbances are very pronounced while the pulmonary disorders are relatively mild. The fourth patient had chronic cor pulmonale (Obs. 50). The fifth was a mitral case who was subject to almost continuous choking without sputum.

Fifth Category: Left Ventricular Insufficiency.—These patients number ten cases: one case of mitral insufficiency, another of calcified aortic stenosis, and eight cases of hypertension.

TREATMENT

Preoperative care, anesthesia, surgery, and postoperative care call for the following remarks. Before surgery nothing should be spared in order to improve the patient's fluid balance by slowing down the heart rhythm and evacuating effusions at the very first. Cardiotonics, water diet without sodium, mercurial diuretics, and sedatives must be administered simultaneously with oxygen-tent therapy, which is practiced systematically.

Spinal anesthesia will allow the creation, for a few hours or a few days, of temporary circulatory conditions very similar to the ones that will be set up after the caval ligation. An intermittent and slow spinal injection of Novocain will bring about a differential sympathetic block which, without affecting motor function or sensitivity, will yield by means of the sympathetic system, remarkable circulatory effects, very similar also to a true spinal-anesthesia or the caval ligation. The patient's system responds remarkably well to such trials but even though the respiratory, cardiac, tensional, and hemodynamic modifications are extraordinarily good their interpretation remains rather difficult.

At first we considered them a truly valid test which enabled us to confirm or cancel the surgical operation already decided upon, and also to direct the prognosis of the operation. If we analyze further the facts we observed and if we try to delve more deeply into their physiopathologic aspects, we believe for the time being that the differential sympathetic block is not so much a test for possible surgery as a desperate therapeutic means permitting a temporary alleviation of the heart stress and the utilization of the last reserves which the myocardium may still possess. Then, taking advantage of this temporary improvement, surgery can be performed with an increased sense of security and, for patients whose general condition is precarious, the postoperative consequences are appreciably reduced.

Anesthesia for patients presenting severe heart failure and for whom the caval ligation is virtually indicated is complex. These patients are usually anoxic, with a deficient myocardium and blood pressure that has already been

considerably lowered. With them, hemorrhage or collapse may have fatal consequences.

The following forms of anesthesia were utilized: rachi-anesthesia 28, cases; rachi-anesthesia and Pentothal, 4 cases; local anesthesia, 23 cases; local anesthesia and general, 16 cases; general anesthesia, 29 cases.

At the present time, the latter form is the most generally used.

Preoperative electrocardiographic control is particularly useful. Various disturbances of heart rhythm take place at the time of intubation. These must be attributed more to anesthesia and parietal reflexes than to the surgery. Moreover, as soon as the ligation of the vena cava is done, it is a good idea to check the effects on the heart.

The operation itself, in spite of its apparent simplicity, is extremely delicate. The retroperitoneal approach which was used at first has now been abandoned for the transparietal, as the latter prevents a serious detachment. The surgeon's task is not easy. He works in a covered region of the body, on edematous tissues and on blood vessels whose walls are fragile. A parietal hemorrhage may always be feared for it is often difficult to check. It seems to us that such accidents happen when anatomic conditions (obesity, kyphosis, ascites) are unfavorable.

Great postoperative care must be taken. A retroperitoneal hematoma is not rare although its seriousness depends on its volume. It can cause extensive detachments with blood effusions to the groins and to the attachment of the diaphragm. Venous thrombosis in the lower limbs is frequently observed. Usually the anticoagulant treatment causes it to disappear rapidly but it has no preventive value. Digitalization of the patients must be continued in a constant and uninterrupted manner; doses must be such as the heart rhythm demands, as this rhythm must be slowed permanently.

RESULTS

In relation to sex and age, our patients are distributed according to Table II.

TABLE II

AGE	UNDER 30	31 TO 40	41 TO 50	OVER 50	TOTAL
Women	5	9	29	11	54
Men	6	11	17	12	46
	11	20	46	23	100

We noted no difference as far as sex was concerned; men and women appear in our statistics with comparable results.

As for age, our youngest patient was a 10-year-old girl who had Ebstein's disease. She was operated on at the insistence of her parents because of her desperate condition. Outside of this exceptional case, surgery was applied only to ten patients under 30. Results were as follows: appreciable improvement, 2 cases; mediocre results, 3 cases; died within the first year, 5 cases.

We are not in favor of the ligation of the inferior vena cava in young adults, considering the clinical course of heart diseases. However, we did meet with a spectacular success in the case of a 30-year-old woman. The course of her disease was stopped and she now leads a normal life. We must also consider a success in another case (Obs. 15) showing signs of marked cardiac insufficiency with cardiomegaly. This patient is now alive, works four hours a day, and rides a motor scooter. His cardiocirculatory equilibrium is maintained with 30 drops of digitalis per day.

One of our young patients died following a retroperitoneal hematoma three years after a temporary period of improvement following an inexorable and complete cardiac insufficiency. The last patient was suddenly stricken with hemiplegia after considerable and sustained improvement in his condition.

On the whole, results in adults, even those who are advanced in years, are more satisfactory even after fifty. Our oldest patient was 63 at the time of surgery and improved notably for the next two years.

The future of our patients after their operation is the one question which holds our greatest attention.

Table III represents the statistics of the progress of these patients. We considered in this table only the fact of their death or survival, in the course of the days, weeks, months and years which followed the caval ligation.

TABLE III. RESULTS FOR THE FIRST YEAR (PATIENTS OPERATED ON, 100)

DEATHS	SURGICAL INDICATIONS				TOTALS	
	TOTAL C.I.	R.V.F.	L.V.F.			
End of first week						
Cardiac insufficiency	2			2		
Retroperiton. hematoma	3	2	1	6		
Mesenteric thrombosis	1			1	13	
Irreducible fainting spell	2	1		3		
Pulmonary edema			1	1		
End of first month						
Cardiac insufficiency	2	1		3	4	
Heparinic shock			1			40
End of first year						
Cardiac insufficiency	8	6	2	16		
Cerebral accident	1	2	1	4		
Irreducible pulmonary edema			1	1	23	
Azygopulmonary anastomosis			1	1		
Repeated emboli		1		1		
Totals	19	13	8	40	40	
Improvements						
Considerable	29	16	2	47	60	60
Relative	5	7	1	13		
Totals	34	23	3	60	60	100

Total C.I. = total cardiac insufficiency. R.V.F. = right ventricular failure. L.V.F. = left ventricular failure.

A distinction must be made, however, between immediate or short range results on the one hand and long range results on the other.

IMMEDIATE RESULTS

An improvement in breathing is the most constant and the most noticeable immediate effect of the operation. We noted it in 80 per cent of the cases. Above all, this immediate improvement takes the form of the disappearance or at least marked diminution of dyspnea due to decubitus. The best way to evaluate this dyspnea is to take account of the number of pillows which the patient requests in order to ease his breathing in bed. After surgery, patients who have been sitting up in bed for months can lie down and sleep without trouble. If they do not like to lie flat on their back, one pillow will be sufficient and in this position they can fall asleep without being awakened by a fit of coughing. This mere fact, although seemingly unimportant, has considerable meaning for the unhappy patients suffering from decompensated hearts who live in constant fear of paroxysmal dyspnea. Accustomed to sleepless nights and to exhausting positions in which the thorax is maintained vertical, they feel great relief in finally being able to lie down. The improvement which they enthusiastically describe is explained by the relaxation of their whole system and the possibility of sleeping normally without choking.

The disappearance or decrease of hepatomegaly is also constantly noticed and takes place within a few hours of the ligation. During the days following, diuresis increases and the renal function tests reveal a better elimination than before the operation.

Radiologically speaking, we habitually observe a marked decrease in the volume of the heart. Is it a true regression of the volume or is it only a resorption of the pericardial effusion so frequently found in such medical cases? The diminution of pulmonary shadows is also a parallel effect and is a natural accompaniment of the disappearance of dyspnea.

On the other hand, an electrocardiogram shows no changes whatever. Arterial pressure falls slightly in hypertensive cases, but this fall is short lived and the same figures appear a few months later. Edema disappears as a rule except if some venous disturbance (anterior phlebitis) was formerly present.

The death rate during operation is relatively high. Cossio had a 20 per cent mortality rate for his first series of patients. Later on, this rate decreased considerably so that in his recent publications he mentions 6 per cent. The best results were obtained by one of his assistants. Out of sixteen patients, no life was lost. We take the term mortality (operative and postoperative) as referring to deaths which occurred during the first week. This length of time, obviously arbitrary, may be questioned. We adopted it however because the causes of death during the first month (except for one special case) seem to us as being connected more closely with late mortality causes than with early ones.

Our own death rate in the course of surgery is about 13 per cent (Table III). Let it be stressed that this over-all figure is quite different from the figures concerning the different stages of our experience. At first, our statistics were show-

ing a 20 per cent death rate while for the last 45 patients (from 55 to 100) we had only three deaths during operation, i.e., 6.6 per cent. Our percentage then exactly corresponds to that of Cossio.

The greatest danger always took the form of a retroperitoneal hematoma. It occurred in six of our postoperative deaths (46 per cent), and consisted twice in the operative injury of the inferior vena cava and four times in progressive hemorrhage arising from dissected zones.

In five other cases, an enormous hematoma appeared but regressed, giving rise to but one complication.

We must blame the death of one of our patients (Obs. 6) on the repercussion of anesthesia on a particularly threatening cardiac insufficiency. This woman who was in a very serious condition had submitted to the spinal anesthesia test and immediately an improvement had without a doubt been noticed. Her breathing was deeper; her cyanosis less marked. A slight regression of hepatomegaly had been observed. In order to take advantage of this improvement, surgery was decided upon the following day and the patient received considerable premedication. As she was wheeled into the operating room, she was already unconscious. Another spinal anesthesia was administered. The patient did not regain consciousness, and her state of collapse persisted. She died the following day. Autopsy revealed no apparent cause for death.

In another case (Obs. 55) death must be attributed to heart failure. Surgery brought no improvement and here again, autopsy could not determine the cause of death.

Heart failure was responsible for the deaths of three patients. In two cases the presence of clots in the pulmonary artery can be incriminated. In the third case, an autopsy was inconclusive.

An acute and irreducible pulmonary edema occurred in the evening following the operation in an aortic patient who had a left ventricular insufficiency. Autopsy confirmed the diagnosis of a calcified aortic stenosis. The increase of the right blood stream could not be assumed by the deficient left ventricle, which, because of the stenosis of the ostium, found itself overburdened instead of relieved.

In one case, we noted signs of acute intestinal obstruction. Autopsy revealed a mesenteric infarction with extensive necrosis. This rare accident seems to bear no direct relation to the ligation of the inferior vena cava.

RESULTS IN THE COURSE OF THE FIRST MONTH (FIRST WEEK EXCEPTED)

For some authors, accidents that took place during the first month are confused with accidents following operation. Yet we feel that a distinction must be made, because in our statistics we think that the natural course of cardiac insufficiency was the cause of three deaths which, for this reason, should not be attributed to surgery.

In one case, cardiac insufficiency was complicated by phlebitis of the leg. This patient showed all the classical signs of acute cor pulmonale. The ligation of the inferior vena cava brought no relief. It even seemed that the increased cardiac output facilitated the appearance of a complete insufficiency.

The second case involves a patient who had been stabbed in the fourth left intercostal space. During the months that followed the accident, a cardiac insufficiency appeared and progressed very rapidly. The presence of a continuous murmur was the manifestation of an arteriovenous aneurysm. In exploratory thoracotomy we were unable to locate the aortopulmonary point of communication. As a consequence, the ligation of the inferior vena cava was performed immediately. The operation brought no improvement to the patient's condition, and he died 17 days later. Since, the aortopulmonary communication yielded an increase in the cardiac output, this case can be declared similar to the one just mentioned.

The third fatal case concerns our youngest patient. After improving for a few days he died of a severe right insufficiency with ascites that rapidly reappeared.

A rare accident happened to the fourth patient of the present group. He was a hypertensive case with a good postoperative course, progressing encouragingly. The appearance of a venous thrombosis (a banal complication in such a case) led to the use of an anticoagulant treatment of intravenous heparin, twenty-six days after the operation. No sooner was the first injection given than the patient was subject to a violent shock. Within two hours he was dead of an irreversible collapse.

RESULTS DURING THE FIRST YEAR (FIRST MONTH EXCEPTED)

A marked improvement has been noted in our patients within a few months of the ligation of the inferior vena cava.

The most striking and impressive change following the operation is the decrease (and occasionally the disappearance) of the respiratory symptoms. However, the patients must be followed closely; cardiac drugs and sedatives must be continued. The edema and liver discomfort and tenderness are markedly reduced and occasionally disappear entirely. Collateral circulation develops slowly. The early appearance of collateral circulation (at the third or fourth month postoperatively) suggests the presence of cirrhosis of the liver antedating the operation. The haziness of the lungs on roentgenologic examination decreases, the cardiac rate is slowed though the electrocardiogram changes but slightly or not at all.

If there is to be lasting benefit, it is essential that the patients be carried successfully through the danger period of the first postoperative year. Cardiac function and output must be restored through rest and medications thus achieving a remission in the evolution of the cardiac pathology.

Examination of our data shows that the mortality is quite high (23 per cent mortality) during this first year. A detailed study of the causes of death leads to the following considerations: (1) In sixteen cases, cardiac insufficiency continued its course. After improvement lasting from a few days to a few months, the general condition of these patients deteriorated and they died of heart failure without remissions, probably because of progressive and irreversible myocardial changes. Caval ligation was without effect, just as medical management was ineffective. We have, however, noted transient improvement of a

few months duration in nine cases, though no improvement whatever was noted in seven cases. As might be anticipated, these were the patients in whom cardiac insufficiency was the most advanced and the least reversible and for whom an early fatal outcome was expected. It was recognized that the odds were against a favorable outcome, but the operation was the last hope for these patients.

(2) In four other cases death was due to a cerebrovascular accident. Three of these patients had improved to such an extent that they had returned to a normal work load and one died with a hemiplegia while at his work bench. Three of these patients had mitral disease; the fourth was a hypertensive. The vascular accidents were evidently not directly related to the caval ligation, but the postoperative improvement in the circulatory disorders which threatened the survival of these patients permitted the eventual fatal progression of the cardiac pathology or of the arterial changes. The mortality in this group of patients cannot, therefore, be ascribed to the caval ligation. However, an opposite and somewhat paradoxical interpretation may be advanced; in preventing death by suffocation and drowning in the edema and effusions, caval ligation has provided the circumstances for death from other causes because of the cardiac pathology. In line with this reasoning, caval ligation is responsible for the vascular accidents, since without this intervention death would have occurred from other causes. Substantial benefit has, however, been derived by the patients from the procedure. Improvement of the dyspnea has occurred and the patient's life has been prolonged. Thus, caval ligation appears to be an essentially palliative procedure as was concluded at its inception by Donzelot, d'Allaines, Heim de Balsac and their collaborators. The effects of this intervention can, therefore, be compared to those of a gastroenterostomy for an inoperable gastric carcinoma.

(3) In another case, there has been noted a persistence of attacks of acute pulmonary edema. This was a hypertensive patient in whom there remained significant sequelae from an infarct. No noticeable improvement followed ligation of the inferior vena cava. It appears that the severely affected left ventricle was unable to perform the work required by an increased cardiac output.

(4) In another patient, caval ligation did not prevent the repetition of pulmonary emboli which had been a deciding factor for the operation. Though an autopsy was not performed, it appears reasonable to suggest that a right auricular thrombosis was responsible for these accidents.

(5) The last observation concerns the case of a 30-year-old man with mitral disease, who had a continuous feeling of suffocation but who had vena cava ligation that was followed by significant improvement. A few months later, further improvement was sought in an anastomosis of the azygos and pulmonary vessels. The patient died three hours postoperatively of intractable acute pulmonary edema.

As a contrast to this examination of the causes of accidents and failures, the data must now be examined with respect to the successful cases. In summary, in the course of the first postoperative year, there have been thirteen deaths at operation, four deaths during the first month, and twenty-three during

the subsequent year, a total of forty deaths. Out of 100 patients, 60 are still living. What is their condition?

Of the sixty survivors, thirteen show but relative improvement and must be considered as no more than partial successes. Nonetheless, this improvement is not negligible. The patients, bedridden, dyspneic, and doomed to an early death, breathe more easily, can get up, and have a less painful existence. Four of these patients died in the course of the second year following caval ligation. In three other patients, survival is longer but activity remains limited. The last three patients in this group have shown a more marked improvement which is, however, considered inadequate in view of the risks to which these patients have been exposed. In these patients, the psychologic disorders which play a large part in the severity of the subjective complaints must be emphasized. This factor should not be neglected in considering the indications for operation; it diminishes the improvement which might otherwise be expected.

There remain forty-seven patients, who, having successfully undergone the operative procedure and its immediate sequelae, have passed through the critical first year under excellent conditions. These are unquestionally cases with successful outcomes, particularly appreciated by the subjects in that at the time of operation they led an incredibly miserable existence. In so far as one may judge in retrospect, there was a serious threat to the survival of these patients, and conventional medical management had shown itself to be relatively or completely ineffective.

These forty-seven patients now have a not unpleasant existence, take care of routine household duties, go out and lead ordinary lives, the only restriction being the avoidance of sudden violent efforts and the only medications being cardiac drugs and sedatives. Many of these patients have returned to their old jobs, at least on a part-time basis, or have learned new trades. They work and thus have been rehabilitated socially.

LATER RESULTS

The data are fewer in number when the later results are examined (Table IV). The high mortality during the first postoperative year and the fact that fewer operations were performed several years ago are the two factors responsible for this decrease in the number of cases.

On examination of these patients at the end of the second, third, and fourth years, it is found that the satisfactory result is maintained in a number of them, the improvement brought about by the caval ligation having permitted them to survive and to take care of themselves.

More than three-fourths of these patients who have survived the first year have remained in good general condition during the second year. A few, however, from time to time present symptoms or signs of cardiac insufficiency with chronic coughs, choking sensations, edema, and cardiac irregularities. These difficulties occur particularly at times when the prescribed diet is not followed

or when the patients undergo unusual physical exertion; they are readily controlled by a return to conventional cardiac management.

This neglect or carelessness on the part of the patients is a result of their improvement; with a return to a normal existence, the patients, in spite of warnings to the contrary, believe themselves to be cured and are no longer concerned with the state of their health.

TABLE IV. RESULTS ON FOLLOW-UP DURING THE SECOND, THIRD, FOURTH AND FIFTH YEARS AFTER LIGATION OF THE INFERIOR VENA CAVA

	INDICATIONS FOR OPERATION			TOTAL
	TOTAL C.I.	R.V.F.	L.V.F.	
Patients operated on 1 year previously = 45				
Died during the second year	2	2	1	5
Did not return for follow-up	1	1		2
Lasting improvement	17	14	2	33
Mediocre results	1	4		5
Totals	21	21	3	45
Patients operated on 2 years previously = 26				
Died during the third year	2	1	1	4
Did not return for follow-up			1	1
Lasting improvement	10	8		18
Mediocre results	1	2		3
Totals	13	11	2	26
Patients operated on 3 and 4 years previously = 12				
Died during the fourth and fifth years		1		1
Did not return for follow-up		1		1
Lasting improvement	4	3		7
Mediocre results	1	2		3
Totals	5	7		12

Total C.I. = total cardiac insufficiency. R.V.F. = right ventricular failure. L.V.F. = left ventricular failure.

Physical examination does not reveal many changes. Auscultation is unchanged. In one patient, however, (No. 17) there has been noted the appearance of an aortic diastolic murmur in addition to the murmur of mitral stenosis detected at the time of operation. Radiologically, an increase in the size of the cardiac shadow is rare. Haziness of the lung fields, studied by comparison of serial roentgenograms, is of prognostic value for the subsequent year if it reappears or increases.

The ECG shows no significant changes. There is no evidence of changes in the liver or kidneys.

There is, however, one factor which, though barely noticeable, is nonetheless important: it is the slow development of a collateral circulation. This allows the blood to return to the right side of the heart without difficulty or with

only slight restraint so that the physiopathologic effects of the caval ligation are gradually diminished. This fact appears to us to determine the prognosis.

The mortality rate during the second year does not exceed 6 per cent, in contrast to the first year when it is 40 per cent. Five patients died during this period; four of these died in heart failure. As previously mentioned, the results were mediocre in three of these patients by the end of the first year. The fourth patient, a 53-year-old woman, died at the end of the second year, after improvement lasting a year and a half. The fifth patient died of a cerebrovascular accident while at his work.

The results considered to be unsatisfactory are concerned with patients whose cases have already been discussed under the first year follow-up.

TABLE V. DISTRIBUTION OF MORTALITY AND PERCENTAGE OF CASES WITH IMPROVEMENT DURING THE FIRST FIVE YEARS FOLLOWING LIGATION OF THE INFERIOR VENA CAVA

DEATH OCCURRED AFTER	LIGATION OF INFERIOR VENA CAVA PERFORMED				TOTAL
	4 AND 5 YR. AGO	3 YR. AGO	2 YR. AGO	1 YR. AGO	
First day	3	1			4
First week	3	3	2	1	9
First month		3		1	4
Sixth month	4	4	5	1	14
1 year	4	3	2		9
2 years	3	1	1		5
3 years	2	2			4
4 and 5 years	1				1
Improvement (important or relative)	10 (33%)	9 (35%)	12 (54%)	15 (83%)	46
Lost to follow-up	3	1			4
Totals	33	27	22	18	100

During the third year, the progression is similar to that of the preceding year. However, collateral circulation develops and decreases the improvement obtained following the ligation. These patients still respond quite well to spinal anesthesia, to cardiac drugs, and to diuretics, if these are indicated. However, the episodes of cardiac failure occur more frequently, evidence of pulmonary congestion becomes more marked, and the heart size tends to increase. The results are nonetheless considered satisfactory since improvement still persists in eighteen of the twenty-six patients (i.e., in 68 per cent) who have survived two years.

Four patients died during the third year because of right and left ventricular failure; the collateral circulation had become fully established, and the general condition of these patients had become similar to that which existed preoperatively. A fourth patient, a hypertensive, died following a fresh myocardial infarction.

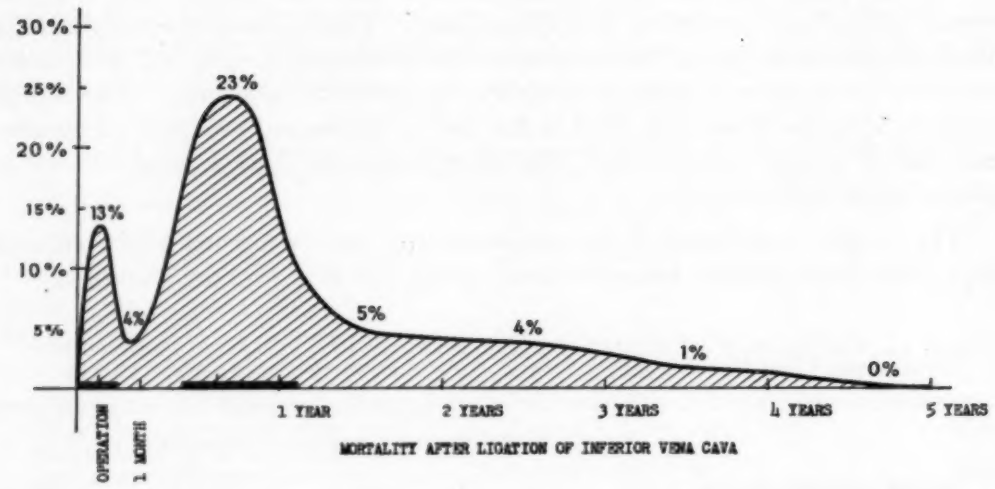

Fig. 1.—Mortality schematic representation during the five years following the vena cava ligation. The mortality is chiefly important at the operative period and during the first year.

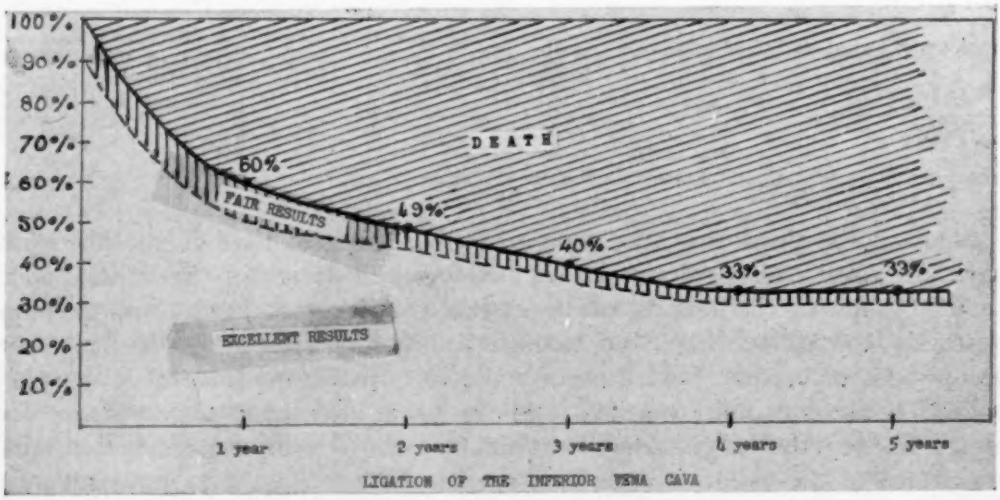

Fig. 2.—Schematic representation of results obtained 5 years after vena cava ligation. Following a high mortality in the first year, the good results obtained faded away slowly, during the following years.

Thirty-three patients underwent the operative procedure four years ago. Of these, fourteen died during the first year and five during the third and fourth years. Three patients have not returned for follow-up: one (No. 4) after 15 months, the other two (Nos. 3 and 27) after three years. Eleven patients have been followed at regular intervals during the four years.

The survival of these eleven patients out of thirty-three subjected to operation established the survival rate at 33 per cent after four years. This result appears to us to be excellent for a palliative procedure. The general condition of these patients is quite satisfactory in eight (72 per cent) and mediocre in three (24 per cent). Our data are affected by the death of one of our patients (No. 2) who had been one of our most successfully treated patients. After having lived and worked normally, this patient died four years postoperatively of an accidental intoxication. From the cardiac standpoint, this case is considered successful.

Among our successful cases, particularly worthy of note is our first patient who leads a completely normal existence and who has never had episodes of failure. Patients in whom mediocre results have been obtained are those already so classified during the course of the third year. Examination of the heart in these patients reveals no changes following the operation. Nor are changes noted on auscultation or on roentgenologic examination. There is neither edema nor ascites. There is no evidence of peripheral collateral circulation.

During the course of the present fifth year of follow-up, no changes have been found in these results noted at the end of the fourth year.

It is considered that the good general condition of these patients depends in part on the care with which the prescribed medical diet has been followed, and in part on the fact that, preoperatively, liver function appeared normal at least within the limits of the tests used.

A summary of the results we have obtained is given in Table V and is shown schematically in Figs. 1 and 2.

SUMMARY AND CONCLUSIONS

In the period between April, 1949, and November, 1953, 100 patients with cardiac decompensation have been treated by ligation of the inferior vena cava at the Medico-chirurgical Center of Broussais. Improvement immediately follows operation. The patient breathes more easily as soon as the ligature is tightened. The regression of the hepatomegaly and the disappearance of the peripheral edema follow and establish the improvement.

There are frequent postoperative complications. Edema of the lower extremities occurs in the presence of old preexisting inflammatory changes in the veins. A cardiac diet must be maintained without interruption following the operative procedure.

The major indications for the procedure are considered to be mitral disease and combined mitral and aortic disease, particularly in patients where rheumatic activity appears to have ceased. Cardiac pathology without valvular lesions and arterial hypertension are also considered to be acceptable indications. Our experience is too limited to assess the results in congenital heart disease.

Absolute contraindications are considered to be cardiac disorders with high output (chronic cor pulmonale, thyrotoxicosis) as well as certain valvular lesions in which marked restriction of the circulation occurs (in advanced aortic stenosis, for example.)

Operation is avoided in patients in whom the cardiac pathology is progressive, a circumstance which occurs particularly in younger patients (less than 30 years old). In these, only partial results are obtained, and the danger of rheumatic progression is greater.

The analysis of our data shows a high mortality during the first postoperative year (23 per cent). This mortality is in part due to a continuation of cardiac degeneration and in part due to the occurrence of vascular accidents. Ligation of the inferior vena cava has no effect on attacks of rheumatic fever or on cerebrovascular accidents.

The mortality diminishes considerably during the second year and remains relatively low after four years. The survival rate after the first year is 60 per cent, after the second 49 per cent, after the third year 40 per cent, and after the fourth and fifth years 33 per cent. These values are distorted by the fact that our operative mortality was too high when this procedure was initiated: 20 per cent was for the first 50 patients as compared to 6 per cent for the next 50 patients.

The duration of the improvement depends on the care with which the patient follows the prescribed medical diet, on the changes in his cardiac pathology, on his liver function, and on his kidney function preoperatively, and on the rapidity with which collateral circulation is established. This last factor appears to destroy the beneficial effects of the operation; cardiac insufficiency reappears and the patient returns to a status similar to that which obtained prior to operation.

Ligation of the inferior vena cava is accordingly considered a satisfactory palliative treatment of intractable cardiac insufficiency particularly when accompanied by the threat of pulmonary emboli. The results of the present procedure correspond to those obtained by means of other major palliative surgical procedures (artificial anus, gastroenterostomy, etc.). The functional improvement achieved and the prolongation of life obtained justify the operative and postoperative risks to the patients.

SUMMARIO IN INTERLINGUA

Es presentate un reporto statistic con commentario de 100 casos de decompensate cardiopathia tractate per ligation del vena cave inferior e observate postoperativemente durante periodos de inter un e cinque annos. Le mortalitate operative es 13 pro cento. Le melioration del circulation cardiac es constante sed varia secundo le condition physic del patiente al tempore del operation. Le duration del melioration es etiam variabile: 27 pro cento del patientes moriva durante le prime anno e 26 pro cento durante le sequente quatro annos, Le remanente 34 pro cento vive e exhibi un melioration satisfacente. Iste

operation palliative es clarmente capace a apportar un notabile alleviamento, mesmo in le pejor casos de dysfunctionamento cardiac. In tal casos le operation es a recommendar.

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EXPERIENCE WITH PHENYLINDANEDIONE IN THE MANAGEMENT OF ACUTE MYOCARDIAL INFARCTION

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SINCE the advent of anticoagulant therapy in thromboembolic disease, a number of preparations have been utilized to gain the desired results. Continuing efforts have been made to find the ideal anticoagulant. Such a preparation should have the following properties: (1) economical, (2) equally utilized and easily administered by any route, (3) consistent effectiveness in per kilo dose, (4) rapid onset of and recovery from the desired effect, (5) quickly controlled by antidote, and (6) free of serious reactions.

Soulier and Gueguen[7] first reported the clinical use of 2 phenyl-1, 3-indanedione as an anticoagulant in 1947. The drug has a coumarin-like action but is not a coumarin derivative. It is reported to have a rapid onset of action, a wide range of therapeutic safety, and few toxic reactions.

This drug† has been used at the Henry Ford Hospital as the routine oral anticoagulant since June, 1953. We are reporting our experience in 251 consecutive cases of proved myocardial infarction to whom the drug had been administered for a minimum of forty-eight hours. These cases were unselected except to exclude those patients in whom any type of oral anticoagulant was contraindicated, as judged by the usual and accepted criteria, and to exclude all those cases receiving the drug for less than forty-eight hours. Therapeutic levels of hypoprothrombinemia were rarely achieved in less time. Seven patients expired less than 48 hours following the initial dose of phenylindanedione and are omitted from this series.

METHOD OF ADMINISTRATION

The initial dose was 300 to 500 mg. given in divided doses in the first twenty-four hours. Subsequent dosage usually varied from 100 to 200 mg. daily also given in divided doses. An occasional patient required smaller or larger daily amounts to maintain the desired hypoprothrombinemia. Dosage was established following a daily prothrombin time determined by the one-stage method of Quick.

Received for publication Dec. 3, 1954.

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†Preparation marketed under trade name of Hedulin, by Walker Laboratories, Inc., Bradford Road, Mount Vernon, N. Y.

Onset of action was usually demonstrable within twenty-four hours. The therapeutic range, 20 per cent to 30 per cent prothrombin activity, was usually reached within forty-eight to seventy-two hours. Prothrombin activity returned to normal within forty-eight to seventy-two hours after the drug was discontinued.

Excessive hypoprothrombinemia, with or without hemorrhage, was readily controlled by omission of one day's dose of phenylindanedione and/or the intravenous administration of emulsified vitamin K_1 oxide. This latter was infrequently required. If employed, small doses were usually sufficient to increase prothrombin activity to a safe therapeutic range. Large doses, given in one single injection, had the undesired effect of increasing prothrombin activity too drastically and leaving the patient refractory to further anticoagulant effect for varying periods up to five days.

MATERIAL

Of the 251 patients, 240 were white, 206 males and 34 females. The remaining eleven were non-Caucasian, nine males and two females.

The majority of the patients were in the sixth and seventh decades of life, ninety-seven in the sixth and 100 in the seventh. There were sixteen patients in the eighth decade, twenty-eight in the fifth, and nine in the fourth decade.

Each infarct was classified, in retrospect, as to severity. Class 1 infarcts, considered mild, included incomplete or subendocardial infarcts accompanied by a slight leukocytosis, elevation of the erythrocyte sedimentation rate, or hyperpyrexia. Class 2 infarcts were moderately severe and comprised transmural infarcts giving rise to significant elevations of the leukocyte count, erythrocyte sedimentation rate, and temperature. Class 3 or severe infarcts comprised those meeting the criteria for Class 2 and having two or more of the following complications: (1) persistent hyperpyrexia of over one week, (2) protracted pain of over twelve hours, (3) prolonged shock of over twelve hours, (4) significant arrhythmia, (5) acute pulmonary edema, or (6) additional thromboembolic phenomenon.

RESULTS

Of all infarctions studied, 188 were initial insults. Of this total, there were forty Class 1 infarcts with thirty-nine recovering. Class 2 infarcts numbered 116, and 110 recovered. The remaining thirty-two were Class 3 infarcts, and twenty-five recovered. Of the 188 patients with initial infarcts, 174 survived, a recovery rate of 92 per cent (Table I).

The remaining sixty-three infarcts were recurrent. Eighteen patients were in Class 1 and all recovered. Twenty-seven patients with Class 2 infarcts were included and twenty-six recovered. Eighteen were in Class 3 and ten recovered. Fifty-four of the sixty-three patients with recurrent infarcts survived, an 86 per cent recovery rate (Table I).

It is therefore demonstrable from a compilation of these figures that 228, 90 per cent of the total infarcts treated, recovered (Table I). This result compares favorably with the recovery of 85.8 per cent of the 189 patients who received bishydroxycoumarin (Dicumarol) reported by Smith and associates[6] from this hospital in 1951.

TABLE I. RECOVERY RATE FROM INITIAL AND RECURRENT INFARCTIONS

TYPE OF INFARCT	CLASS	NO. OF CASES	RECOVERIES	
			NO.	(%)
Initial	1	40	39	97.5
	2	116	110	94.8
	3	32	25	78.0
Total initial		188	174	92.0
Recurrent	1	18	18	100.0
	2	27	26	96.0
	3	18	10	55.5
Total recurrent		63	54	86.0
Total infarctions		251	228	90.0

COMPLICATIONS

Despite anticoagulant therapy three patients extended their original infarct, and one patient developed a new one. The latter was sustained by a patient with polycythemia vera who developed a new anterior infarct while being treated for an initial posterior infarct. It is interesting to note that this patient had a hematocrit of 62 per cent twenty-four hours previous to the new insult. The patient subsequently made an uneventful recovery. The remaining three extended their original infarct, two expiring within twenty-four hours of the extension and the third recovering.

Thromboembolic episodes involving other regions of the body occurred in five instances. Pulmonary artery embolism with pulmonary infarction was encountered three times with one fatality. One patient, sustaining his myocardial infarction following cholecystectomy for a gangrenous gall bladder, subsequently had an embolus to the left common iliac, and right femoral and popliteal arteries. This patient expired the day following embolectomy. Another patient suffered embolization of a brachial and a cerebral artery in addition to a pulmonary artery and subsequently recovered.

Nine cases of thromboembolic complications, 3.5 per cent of the total, involving both additional myocardium and distal vessels, are reported (Table II). This represents a reduction of approximately 50 per cent of similar complications reported in the previously mentioned series treated with bishydroxycoumarin.

TABLE II. THROMBOEMBOLIC COMPLICATIONS

LOCATION		NO.	(%)	RESULTS	
				RECOV.	EXP.
Myocardium	New infarct	1	0.4	1	
	Extension of orig. infarct	3	1.2	1	2
	Total involving myocardium	4	1.6	2	2
Distal arteries	Pul. emb. with pul. infarct	3	1.2	2	1
	Emb. of lft. common iliac, rt. femoral and popliteal art.	1	0.4		1
	Emb. of brachial, cerebral and pulmonary arteries	1	0.4	1	
	Total involving distal arteries	5	2.0	3	2
	Total thromboembolic complications	9	3.5	5	4

The physician must accept the calculated risk of excessive hypoprothrombinemia in any patient receiving anticoagulants. Such excessive levels, within themselves, do not constitute contraindications to the use of any given preparation. Neither does such indicate more than a temporary omission of the drug in most cases. It has been our repeated experience that a sudden rise is not fraught with any great danger unless the level is allowed to remain excessive for a protracted length of time. A concurring opinion was recently expressed to one of the authors by Dr. Frank Mann, Jr.[4] of the Mayo Clinic. Our practice has been to omit the drug for twenty-four hours when such excessive levels are inadvertently reached. Failing a return to a more desirable level within this time, a small dose, usually 3 to 5 mg., of emulsified vitamin K_1 oxide was administered intravenously. This amount proved satisfactory for our purposes. It would increase prothrombin activity toward a more desirable level but would not leave the patient refractory to further phenylindanedione administration. This latter property was frequently observed with larger amounts of the drug.

Minor, nonfatal complications due to hypoprothrombinemia, consisting of bleeding which cleared spontaneously, were observed in nine cases. Four complained of epistaxis, four of gross hematuria, and one of hematemesis. Only in the case of hematemesis was it deemed advisable to discontinue the drug. Recurrence of this type of complication was not encountered in any of these cases.

One major, nonfatal hemorrhage occurred. This patient had melena of a magnitude requiring immediate injection of emulsified vitamin K_1 oxide, and transfusion of one liter of blood. The patient responded promptly and subsequently recovered. Anticoagulants were permanently discontinued in this patient. Prothrombin activity previous to hemorrhage was less than the desired therapeutic level.

Three major hemorrhages associated with death were encountered. One fatality followed hemorrhage into and rupture of a chronically inflammed gall bladder with resulting bile peritonitis and shock. The patient expired following surgery while still in shock although hemorrhage had been brought under control. The second patient suffered an extensive cerebrovascular hemorrhage the second day following admission and expired. Prothrombin activity was within the desired therapeutic range in both of these patients at the time of their accidents. While hypoprothrombinemia was a contributing factor in their deaths, we do not believe it was the direct, causative factor. The third fatality occurred in a patient who developed gross hematuria and melena. Despite supportive measures the patient expired. Focal hemorrhages of the gastrointestinal tract were demonstrated at necropsy. This death was probably a direct result of hypoprothrombinemia.

In all, thirteen cases, 5.2 per cent, of hemorrhagic complications were encountered (Table III). This compares well with the usually reported incidence of this complication.

TABLE III. HEMORRHAGIC COMPLICATIONS

TYPE	LOCATION	NO.	(%)	RESULTS	
				RECOV.	EXP.
Minor	Epistaxis	4	1.6	4	
	Hematuria	4	1.6	4	
	Hematemesis	1	0.4	1	
	Total minor hemorrhage	9	3.6	9	
Major	Melena	2	0.8	1	1
	Gall bladder hemorrhage with rupture	1	0.4		1
	Cerebral	1	0.4		1
	Total major hemorrhage	4	1.6	1	3
	Total hemorrhagic complications	13	5.2	10	3

Two cases treated with phenylindanedione developed a purpuric maculopapular eruption within forty-eight hours of the initiation of therapy. The eruption was interpreted as a drug rash and disappeared within one week of the termination of phenylindanedione. No additional tendency toward bleeding was observed. These cases are not included in this series, insufficient time having elapsed for the anticoagulant effect to be evaluated before the drug was discontinued.

Brown and MacMillan[2] reported agranulocytosis due to phenylindanedione in two of their patients. Makous and Vander Veer[3] report one case of drug

sensitivity in which hepatitis, jaundice, a leukemoid blood picture, skin rash, and anemia were noted. No such reactions were observed in any of our cases.

Annoying side reactions to the drug were common and were relegated to occasional complaints of nausea following ingestion of the initial dose. As this occurred while the patient was undergoing the emotional and physical shock incident to a myocardial infarction, the reaction is somewhat difficult to evaluate. However, it would seem that phenylindanedione was a causal agent in some of the cases. The distress subsided in twelve to twenty-four hours and discontinuation of the drug was not required in any case.

A misleading side effect is the pinkish orange discoloration imparted to an alkaline urine. This is occasionally misinterpreted as hematuria. However, it is of no pathologic significance being due to the chromatic properties of the drug in a medium of alkaline pH.

COMMENTS

There have been several favorable reports[1,5,8,9] of the use of phenylindanedione in the treatment of thromboembolic disease. Our experience confirms its value as applied to the management of acute myocardial infarction.

The drug has the most rapid onset of action of any of the oral anticoagulants. The therapeutic range of hypoprothrombinemia was relatively easy to induce and maintain, although dosage varied moderately from patient to patient. Prothrombin activity returns rapidly to normal following discontinuation of the drug. Excessive hypoprothrombinemia may be readily controlled by a brief period of drug omission and/or small to moderate doses of emulsified vitamin K_1 oxide. No instance of drug resistance was encountered.

The drug was equally effective in all cases regardless of sex, age, or race.

The incidence of thromboembolic complications despite proper anticoagulant therapy is less with phenylindanedione than with any other anticoagulant employed in a similar role by this clinic.

Hemorrhagic complications incident to the use of this drug were, for the most part, minor. Nevertheless, two deaths in which hypoprothrombinemia played a definite role, and one in which it was probably the cause are reported. However, the over-all incidence of hemorrhagic complications was well within the expected range.

Sporadic instances of grave complications due to idiosyncrasies to the drug have been reported. No such reactions were encountered in our series, although two cases of skin eruption are recorded. It would seem that such grave reactions are uncommon, but awareness of their possibility should be appreciated.

It is interesting to note that the usually increased fatality rate associated with recurrent infarction was not noted in this series.

Based upon our experience phenylindanedione is not the ideal anticoagulant. It is, however, equal or superior to other oral preparations in general use in the anticoagulant therapy of the acute phase of myocardial infarction.

SUMMARY

A series of 251 cases of acute myocardial infarction treated during the acute phase with phenylindanedione is reported. All cases treated for less than 48 hours are excluded. The over-all recovery rate was 90 per cent. The incidence of thromboembolic complications was 3.5 per cent. Major hemorrhagic complications occurred in only 1.6 per cent of the total cases. Two cases of skin eruption requiring the immediate discontinuation of the drug were observed. It is our belief that, at present, this is the oral anticoagulant of choice.

SUMMARIO IN INTERLINGUA

Es reportate un serie de 251 casos de acute infarctos myocardiac tractate durante le phase acute con phenylindanediona. Le serie esseva non-seligite excepte que illo non includeva (1) ulle patiente pro qui omne typo de anticoagulante oral es contraindicate e (2) ulle patiente qui recipeva le droga durante minus que 48 horas. Le recovrage total amontava a 90 pro cento. Complicationes thromboembolic occurreva in 3,5 e major complicationes hemorrhagic in 1,6 pro cento del casos. Esseva notate duo casos de eruptiones dermatic que necessitava le immediate interruption del uso del droga. Nos crede que al tempore presente phenylindanediona es le anticoagulante oral de preferentia.

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EFFECTIVENESS OF ARAMINE* IN THE TREATMENT OF SHOCK

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THE value of vasopressor agents as collateral therapy for the treatment of shock of various etiologies[1-5] appears to be well documented. Pressor agents are not only effective in restoring blood pressure, but certain of the agents have been shown to be equally effective in improving depressed renal function.[6,7] Aramine, a synthetic sympathomimetic amine, is one of the more recent of the vasopressor agents to be investigated. Like phenylephrine, it falls into the group of M-hydroxyphenylalkylamines. In contrast to the evanescent action of norepinephrine, the duration of action of Aramine is more prolonged. Observations on the cardiovascular and renal hemodynamic effects of Aramine in normal subjects revealed minimal renal vasoconstriction, no increased cardiac rhythmicity, and no appreciable change in cardiac output.[8] These attributes led to its evaluation in the management of clinical shock.

METHODS AND PROCEDURE

Aramine was administered by constant intravenous infusion to twenty patients in clinical shock of various etiologies. The concentration varied from 50 to 200 milligrams per liter, depending upon the pressor response. The rate of infusion was varied (between 2 and 6 c.c./min.) as necessary in order to avoid excessive fluid administration. In four of the twenty patients, norepinephrine in concentrations varying from 4 to 16 milligrams per liter was used in combination with Aramine in an attempt to maintain a constant blood pressure without administering large amounts of fluid. The other patients were treated alternately with Aramine and norepinephrine (for shorter periods of time) for comparative purposes. Renal hemodynamic studies were done on several patients using inulin to determine glomerular filtration rate and para-aminohippurate to determine renal plasma flow.

The average age of this group of patients was 63 years, with a range from 23 to 93 years. There were fourteen males and six females. Shock was due to acute myocardial infarction in three patients, cerebrovascular accident in four, upper gastrointestinal hemorrhage in one, bleeding esophageal varices in two,

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Supported in part by grants from the Houston Heart Association and the National Heart Institute, U. S. Public Health Service.

Received for publication Dec. 3, 1954.

*Aramine is levo 1-(M-hydroxyphenyl)-2-amino-1-propanol.

serum sickness in one, post-partum hemorrhage in one, uremia in three, Weil's disease in one, sickle-cell crisis in one, carcinomatosis in two, and anesthesia induction in one. Six of the patients received whole blood transfusions in varying amounts prior to the vasopressor administration.

RESULTS

The results obtained are summarized in Table I. It is estimated that all of these patients probably would have died had not vasopressor therapy been available. Nineteen of the patients had a prompt and satisfactory vasopressor response within eight to ten minutes. The unresponsive patient (No. 20) was admitted in shock of approximately 2½ hours' duration. Despite rapid intravenous administration of Aramine in a concentration of 200 mg./L., there was no significant blood pressure response, and the patient expired 13½ hours later. The duration of vasopressor therapy for the group of patients lasted from 5 hours to as long as 231½ hours* (Aramine 165½ hours and norepinephrine 66 hours). In the latter patient, repeated attempts were made to discontinue the vasopressor agents and in each instance hypotensive levels promptly ensued and persisted until the infusion was again started. The patient finally died when the infusion was inadvertently discontinued due to inadequate nursing supervision.

Despite the fact that fourteen of the patients expired, a satisfactory blood pressure response was obtained in all except one patient (No. 20) for considerable periods of time. Of the thirteen patients who died despite an adequate initial blood pressure response, six maintained an adequate blood pressure until a few minutes prior to death. One patient (No. 19) was maintained on a combination of Aramine and norepinephrine for a period of 10 days, and death ensued only when the vasopressor agents were inadvertently discontinued. Ten of the fourteen patients who expired received Aramine as the only pressor agent†, while four were treated with a combination of norepinephrine and Aramine.

When the responses to Aramine and norepinephrine were compared, using each drug alone, it became apparent that on a weight basis Aramine was only about 1/20 to 1/25 as potent as norepinephrine when administered by continuous intravenous infusion to patients in shock. However, the blood pressure was much easier to maintain at a constant level than with norepinephrine, and the frequency of blood pressure determinations could thereby be decreased. The combination of Aramine and norepinephrine similarly resulted in a more potent vasopressor response with less fluctuations in blood pressure than when norepinephrine was used alone. When Aramine was used alone in the concentrations indicated, no cutaneous sloughs resulted from intravenous administration of Aramine into peripheral veins although several extravasations occurred during therapy. However, when it became apparent that prolonged vasopressor administration would be necessary, a polyethylene tube was inserted into the

*Patient W.O.W. (No. 19).

†Except when potency comparison studies with norepinephrine were being made.

TABLE I. CLINICAL MANIFESTATIONS OF

PATIENT	AGE	SEX	ETIOLOGY OF SHOCK	DURATION OF SHOCK BEFORE THERAPY	INITIAL	
					BLOOD PRESSURE	PULSE
1. T.W.	93	M	Malnutrition, electrolyte imbalance	2 hr.	70/40	100
2. J.H.	51	M	Uremia	30 min.	?	88
3. L.H.	70	M	Myocardial infarction, vent. tachycardia	15 min.	58/46	84
4. A.S.	66	F	Serum sickness	?	70/40	110
5. V.M.W.	23	F	Post-partum hemorrhage	60 min.	?	180+
6. V.S.	44	F	Bleeding esophageal varices	2 hr.	60/40	94
7. N.J.	78	F	Cerebral hemorrhage	?	55/35	130
8. J.T.	84	M	Uremia, upper GI	5–6 hr.	80/40	88
9. C.C.	43	M	Bleeding esophageal varices	7 hr.	60/30	112
10. D.S.L.	72	M	Carcinoma of head of pancreas	?	80/50	96
11. M.S.	51	F	Cerebral hemorrhage	20 min.	100/70	144
12. G.F.C.	88	M	Myocardial infarction	?	80/50	86
13. W.W.	28	M	Sickle-cell crisis	1½ hr.	50/20	100
14. W.J.	52	M	Uremia	1½ hr.	74/58	122
15. G.P.	64	F	Weil's disease. Hepatic failure	2 hr.	68/40	96
16. P.O.	63	M	Cerebral hemorrhage	8 hr.	80/50	108
17. C.A.B.	51	M	Induction of anesthesia	60 min.	70/40	80
18. M.A.	74	M	Myocardial infarction	45 min.	80/50	130
19. W.O.W.	78	M	Cerebral thrombosis	2 hr.	70/50	?
20. B.H.	80	M	?	2½ hr.	70/?	118

femoral vein using a 13-gauge needle. The tube was extended up into the inferior vena cava. This particular technique has been used repeatedly with norepinephrine and Aramine with no evident ill effect even after 8 to 12 days of continuous vasopressor administration.

When the blood pressure was restored to normal levels, there appeared to be improvement in compromised renal function as manifested by onset of adequate urinary output in patients who previously showed oliguria. This was confirmed in several instances by observing the effect of Aramine administration on renal hemodynamics. Similarly, the state of consciousness appeared to be improved when normal blood pressure was restored. Aramine administration was attended by a reduction in cardiac rate in all except two of the patients treated.

SHOCK AND THE RESPONSE TO ARAMINE

DURING TREATMENT		ARAMINE CONCENTRATION IN MG./L.	DURATION OF THERAPY IN HOURS	REMARKS
BLOOD PRESSURE	PULSE			
100/50	90	50–80	26	Expired. Gradual decrease in blood pressure in spite of increasing concentration of Aramine in infusion.
110/80	97	60–120	10	Expired. Malignant hypertension. Terminal state.
110/80	70	50	51½	Recovered. Ventricular tachycardia converted prior to Aramine therapy.
130/86	78	80	20	Recovered.
60/? to 120/70	130	150		Recovered. Shock followed delivery of triplets.
90/70	98	100	24	Portal cirrhosis with bleeding esophageal varices.
110/70	90	120	25	Blood pressure stabilized after 15 hr. treatment.
110/50	80	70	41½	Expired. Blood pressure continued to decrease in spite of increasing concentration of Aramine and norepinephrine.
115/60	100	50	32	Expired. Blood pressure continued to decrease in spite of increasing concentration of Aramine and norepinephrine.
130/100	88	50	20	Expired. Blood pressure continued to decrease with increasing concentration of norepinephrine and Aramine.
135/100	120	100–200	72½	Expired. Aramine gradually increased up to 200 mg./L. in an attempt to maintain blood pressure.
110/60	60	100	165½	Recovered. Maintained on Aramine infusion for 66 hr.
98/60	96	60–120	15	Expired: Never recovered from shock state.
110/90	100	80	32½	Expired. Carcinomatosis. Urethral transplants. Cardiac arrest with massage. Blood pressure maintained for 32½ hr. with Aramine.
110/70	92	60–100	36	Expired. Patient admitted in coma.
110/70	84	60–200	106	Expired. Unable to maintain blood pressure with increasing concentration and rate of infusion of Aramine.
120/60	64	60	5	Recovered. Patient had carcinoma of tongue.
130/90	98	100	14	Blood pressure adequately maintained.
135/80	140	50–60	10 days	Patient expired when combination of norepinephrine and Aramine inadvertently discontinued.
80/40	100	60–200	13½	Admitted in shock and patient never responded.

CASE REPORTS

Patient A. S., a 66-year-old Negro female, came to the Medical Clinic complaining of generalized pruritus, hives, and dizziness and "passing out spells" for the past 24 hours. She had been seen in the emergency room six days previously because of a puncture wound of her right hand caused by a fish fin, at which time she was given tetanus antitoxin and penicillin injections. Physical examination was essentially negative except for lethargy, facial edema with puffiness of the eyes, and generalized urticaria and shock. Her blood pressure was 70 mm. Hg systolic and 40 diastolic.

An intravenous infusion containing 80 mg. Aramine per liter of 5 per cent glucose was begun and within ten minutes her blood pressure was restored to normal limits and the infusion rate was adjusted so as to maintain the desired blood pressure (Fig. 1). Another infusion containing 20 mg. of ACTH was begun intravenously and infused at a very slow rate. After three hours of Aramine therapy, an attempt was made to discontinue it without success. The infusion was

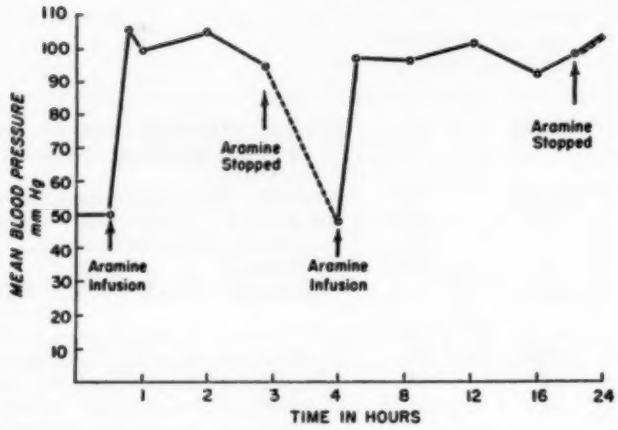

Fig. 1.—Blood pressure response to Aramine, patient A.S., No. 4.

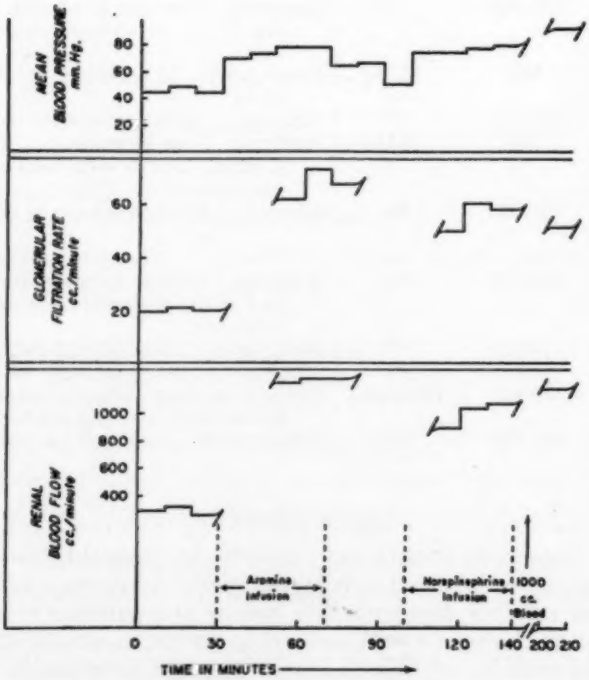

Fig. 2.—Renal hemodynamic response to Aramine and norepinephrine. As the blood pressure is returned to normal, glomerular filtration rate and renal blood flow return toward normal.

again started and the blood pressure was returned to a normotensive level. Frequent attempts were made to discontinue the vasopressor agent but without success during the next 20 hours of continuous infusion. Subsequent to this, the blood pressure stabilized at normal levels without therapy. Following the administration of ACTH, the urticaria cleared rapidly, and the patient was discharged fully recovered on the sixth hospital day. The only noticeable ill effect from Aramine therapy was some pain at the infusion site. There was no evidence of cellulitis.

Patient V. S., a 44-year-old female, was admitted to the hospital with the diagnosis of chronic alcoholism, portal cirrhosis, hepatic coma, bleeding esophageal varices, and peripheral circulatory collapse. She had been known to have had cirrhosis for a number of years and had had five previous episodes of bleeding from esophageal varices between 1949 and 1953. The splenic artery was ligated at another hospital in 1952.

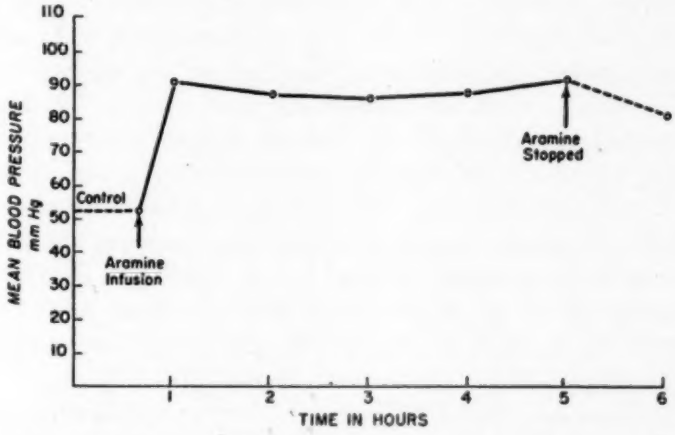

Fig. 3.—Blood pressure response to Aramine when given to patient C.A.B., No. 17.

Initially the patient received 1,000 c.c. of whole blood intravenously, following which her blood pressure stabilized at 100/50 mm. Hg. Because of persistent bleeding, an esophageal balloon was inserted and for a time it appeared that bleeding had ceased. In spite of vigorous supplementary therapy, esophageal bleeding again began after 24 hours, and 1,000 c.c. more of whole blood was infused. The blood pressure gradually began to decrease, at which time she was placed on Aramine (100 mg./L.) adjusted at a rate so as to maintain a blood pressure of approximately 100/60 mm. Hg. Differential renal function studies were done using Aramine, norepinephrine, and whole blood infusion alternately for comparison (Fig. 2). After 24 hours of Aramine therapy, in spite of increasing rapidity of vasopressor administration and partial blood replacement, the blood pressure gradually decreased and the patient expired. Each time during the period of Aramine therapy that an attempt was made to discontinue it, the blood pressure dropped rapidly to shock levels. Norepinephrine was also tried in this patient during the terminal period but this was likewise ineffective.

Patient C.A.B., a 51-year-old white male, was admitted to the hospital with a diagnosis of cervical metastases of squamous cell carcinoma from a primary lesion in the tongue which was previously treated by radium implants and external radiation. He was admitted for a radical neck dissection. The past history revealed several previous hospital admissions because of portal cirrhosis with ascites and peripheral edema. Physical findings revealed a 1.5 cm. defect at the base of the tongue, a firm anterior cervical lymph node 1.0 cm. in diameter, and hepatomegaly, with the liver edge palpable 8 cm. below the right costal margin.

During anesthesia induction, the patient's blood pressure fell to 70/40 mm. Hg. The anesthesia was discontinued. Surgery was postponed except for excision biopsy of a node, and Aramine (60 mg./L. of 5 per cent glucose) was begun. There was gradual increase in blood pressure to normotensive levels where it was maintained (Fig. 3). After five hours, the blood pressure stabilized, and Aramine was discontinued.

DISCUSSION

Aramine (levo 1-(M-hydroxyphenyl)-2-amino-1-propanol) is a synthetic sympathomimetic amine. As is true with most other sympathomimetic amines, the usual manifestations of toxicity are only exaggerations of pharmacologic properties of the drug. Under experimental conditions in anesthetized dogs, Aramine is about 1/20 as potent as epinephrine in producing a pressor response, but the duration of this response was like that seen with ephedrine. These observations have been confirmed clinically in the current report when Aramine was used for the treatment of shock.

Cardiovascular Response.—The cardiovascular response to Aramine has been studied extensively in dogs by Sarnoff and associates.[9] In normal animals, Aramine administration intravenously resulted in an elevation of the mean arterial blood pressure with an associated bradycardia. Presumably, reflex mechanisms limited elevation of the arterial blood pressure. Similar observations following vagotomy resulted in a more marked pressor effect. Aramine administered intravenously to dogs previously rendered hypotensive by phlebotomy resulted in a pressor response without bradycardia until the blood pressure had returned to or exceeded normal levels. In doses of 0.05 mg./kilogram body weight administered to vagotomized dogs, Aramine produced an increase in cardiac output, an increase in coronary artery blood flow, and an increase in aortic and pulmonary artery pressures. Right and left atrial pressures fell. Larger doses of Aramine caused no sign of a further increase in cardiac output but a marked increase in aortic pressure which resulted from the intense pressor response.

Cardiac output studies in normal human subjects[8] showed no change following the administration of Aramine. As the blood pressure increased, there was a parallel increase in peripheral resistance without a significant effect on cardiac output. The cardiac output was not altered despite a significant reduction in pulse rate. The effect of Aramine administration to patients in shock has not been studied.

Renal Effects.—Moyer and associates[6] demonstrated that dogs previously rendered hypotensive by phlebotomy showed improved renal function when the blood pressure was restored to normotensive levels. This was manifested by increased urinary output, glomerular filtration rate, and renal blood flow. On the contrary, when differential renal function studies were done in nine normal humans rendered hypertensive by intravenous Aramine, there was no significant alteration of glomerular filtration rate, a slight reduction in renal blood flow and a moderate increase in renal vascular resistance.[8] Restoration of blood pressure to normal by intravenous administration of Aramine to patients in clinical shock (in the current report) resulted in marked improvement in compromised renal function (Fig. 2). The improvement was manifested by increases in glomerular filtration rate, renal blood flow and urine volume.

Central Nervous System Effects.—No definitive studies have been done on cerebral blood flow in patients with shock who were treated with Aramine. Clinical observations, however, indicate that there is beneficial effect as mani-

fested by improvement in the state of consciousness. Cerebral blood flow is depressed in patients rendered hypotensive by a ganglionic blocking agent (Fig. 4), and Aramine administered intravenously for restoring blood pressure to normal is effective in increasing cerebral blood flow.[10] This, of course, cannot be assumed to be the same response as occurs in clinical shock, but certainly it is suggestive. When normal subjects were rendered hypertensive by an infusion of Aramine, cerebral blood flow was not depressed significantly and cerebral oxygen uptake was not altered.[10]

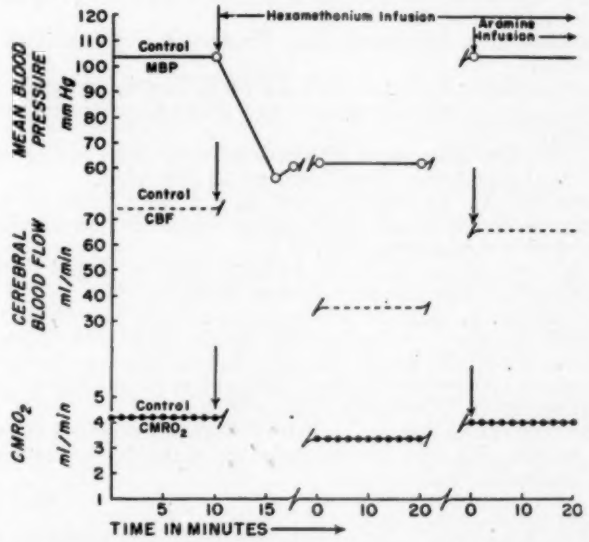

Fig. 4.—Cerebral hemodynamic response to blood pressure reduction to hypotensive levels with hexamethonium and the effect of increasing the blood pressure to normotensive levels with Aramine. Reprinted by permission from Moyer, J. H., Morris, G., and Snyder, H.: Circulation **10**:269, 1954.

Side Effects.—In this group of patients there were no evident ill effects from Aramine administration. One patient complained of pain at the injection site, but no cellulitis or slough occurred.

CONCLUSIONS

Aramine is usually effective in restoring and maintaining blood pressure in clinical shock due to numerous causes. It appears to have some advantage over norepinephrine in that its action is not so evanescent as norepinephrine and thereby permits maintainance of a more stable blood pressure. No sloughs resulted from its use intravenously. Compromised renal function is improved in that there is an increase in glomerular filtration rate, renal blood flow, and urinary output.

SUMMARIO IN INTERLINGUA

Aramina es usualmente efficace in restaurar e mantener pression sanguinee in choc clinic ab numerose causas. Illo pare haber certe avantages supra norepinephrina in tanto que su action es minus evanescente e ergo permitte man-

tener un plus stabile pression del sanguine. Su uso intravenose non resultava in ulle cellulitis o sphacelo. Un compromittite function renal es ameliorate per Aramina in tanto que il occurre un augmentation del filtration glomerular, del fluxo de sanguine renal, e del rendimento urinari.

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Clinical Reports

LUCIANI PERIODS IN MAN CAUSED BY PROCAINE AMIDE

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LUCIANI[9] demonstrated in 1873 that an isolated frog heart in which the sinus venosus was separated from the ventricles by a Stannius' ligature developed periods of cardiac standstill in which there appeared series of grouped cardiac contractions. A characteristic of these groups was that the interval between the cardiac contractions, relatively long at first, became shortest in the middle of the period, and increased again toward the end.

Wenckebach[10] first described a similar formation of grouped cardiac contractions in man. After this publication in 1908, nothing was published in reference to these "periods of Luciani" for a long time. In the Netherlands about 1930, renewed attention was given to these so-called "periods of Luciani" by the experimental work of van Ginkel[4] and de Boer and associates.[2] This resulted in reports of cases with the bizarre disturbance of rhythm by several Netherlands clinicians.[2-4,7]

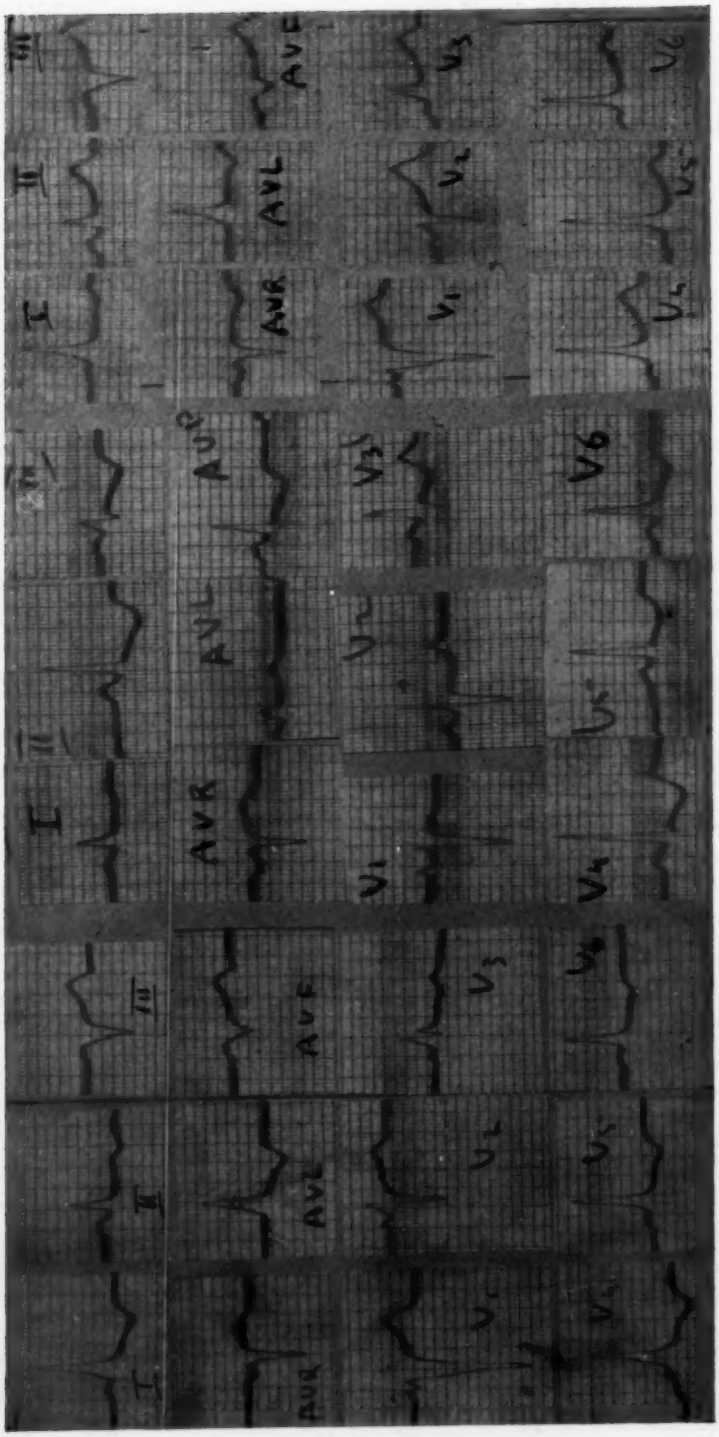
Van Ginkel[4] considered the separation of the atrium (auricle) from the ventricle as an absolute condition for the occurrence of this phenomenon. He was inclined to believe that anoxia promoted this abnormality but that the formation of grouped beats could also be observed in the absence of tissue asphyxia. De Boer[2] believes that he demonstrated in his experiments that the formation of Luciani periods was also possible with sinus rhythm, and he observed the groups of contractions during nodal rhythm also. Van Ginkel explained the phenomena by the coexistence of continuous increasing and decreasing excitability and stimulus formation.

We observed in one of our patients episodes of grouped cardiac contractions in agreement with these criteria. These Luciani periods occurred during the treatment of attacks of paroxysmal tachycardia with intravenous procaine amide. During the attack of paroxysmal tachycardia a nodal rhythm existed, and therefore the influence of the sinus node can be considered to have been absent. Furthermore, it may be concluded that some anoxia of the heart muscle probably also existed.

CASE REPORT

A married woman, aged 22, was first examined in 1939 when she developed attacks of paroxysmal tachycardia. She had had no previous illnesses. At the first examination the initial electrocardiogram revealed the syndrome of Wilson-Wolff-Parkinson-White, (W-W-P-W), with

Received for publication July 26, 1954.



A. *B.* *C.*

Fig. 1.—*A*, Wolff-Parkinson-White syndrome. Electrocardiogram made a week after the termination of an attack of two days' duration. *B*, Electrocardiogram shows normal conduction made after an attack treated with various drugs among them procaine amide. Note the changes in the S-T segment, the post-tachycardia syndrome. *C*, Wolff-Parkinson-White syndrome recorded direct after a short attack, ending spontaneously. Note the absence of the post-tachycardia syndrome.

shortening of the P-R, widening of the QRS, slurring of the first portion of the QRS and changes in the T wave and S-T segment. It was possible in this patient to compare these findings with the pattern recorded during normal A-V conduction which occasionally occurred in this patient. The time intervals noted during the W-W-P-W syndrome were P-R, 0.08 second and QRS, 0.10 second. During the time of normal A-V conduction they were P-R, 0.10 to 0.14 second and 0.08 second for the QRS.

From 1939 until the present, the patient has complained of attacks of rapid heart action and palpitation. The attacks were usually precipitated by emotion, exercise, and the onset of menstruation but also developed without any conspicuous cause. The paroxysms lasted from a few hours to as long as nine days. In the more prolonged attacks, shortness of breath, cyanosis, liver engorgement, and dilatation of the heart gradually developed, and the blood pressure fell. At the end of such a prolonged attack the electrocardiogram showed signs of the so-called "post-tachycardia syndrome" with marked T-wave inversion. The ECG then resembled that of the subacute stage of myocardial infarction, which could be explained by exhaustion anoxia of the heart muscle (Fig. 1, *A* and *B*). After short attacks the S-T segments and T waves remained normal (Fig. 1, *C*).

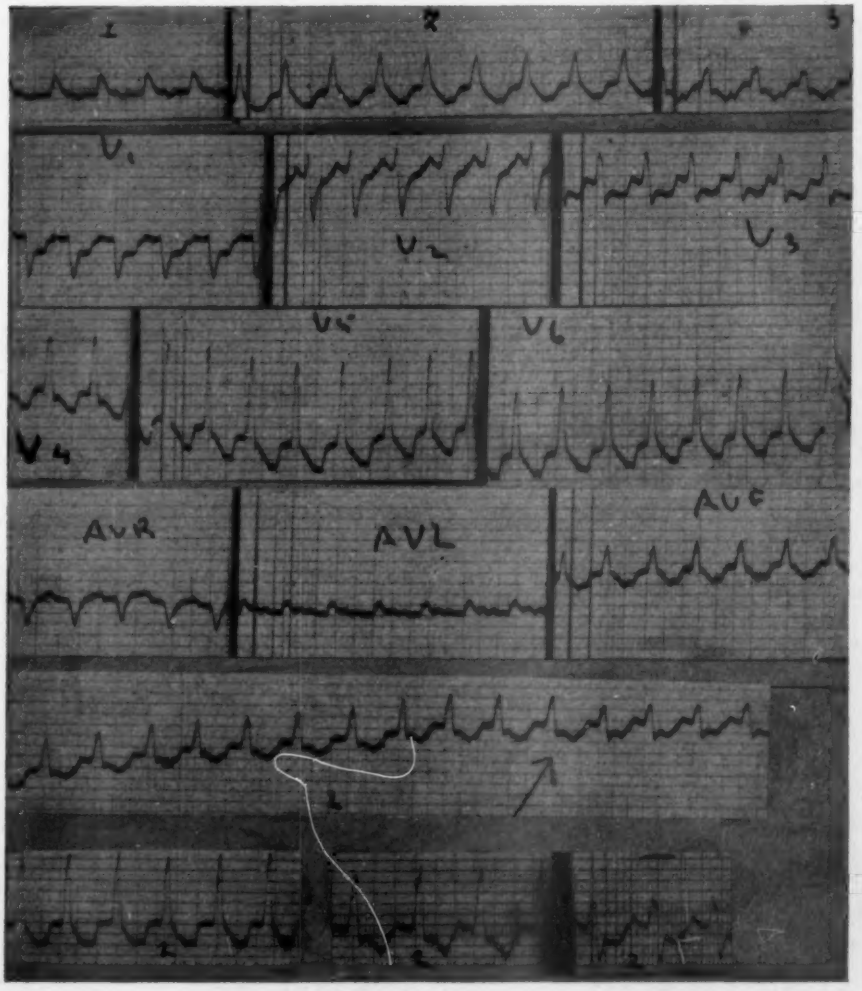


Fig. 2.—*A*, *B*, *C*, and *D*, Attack of paroxysmal tachycardia. Note in Leads I, III, aV_L and aV_F, P waves following QRS. *E*, Lead II, one minute after 400 mg. procaine amide, intravenously. Arrow indicates change of the QRS complex. *F*, Lead II, Note the decrease of rate and the change of QRS caused by procaine amide.

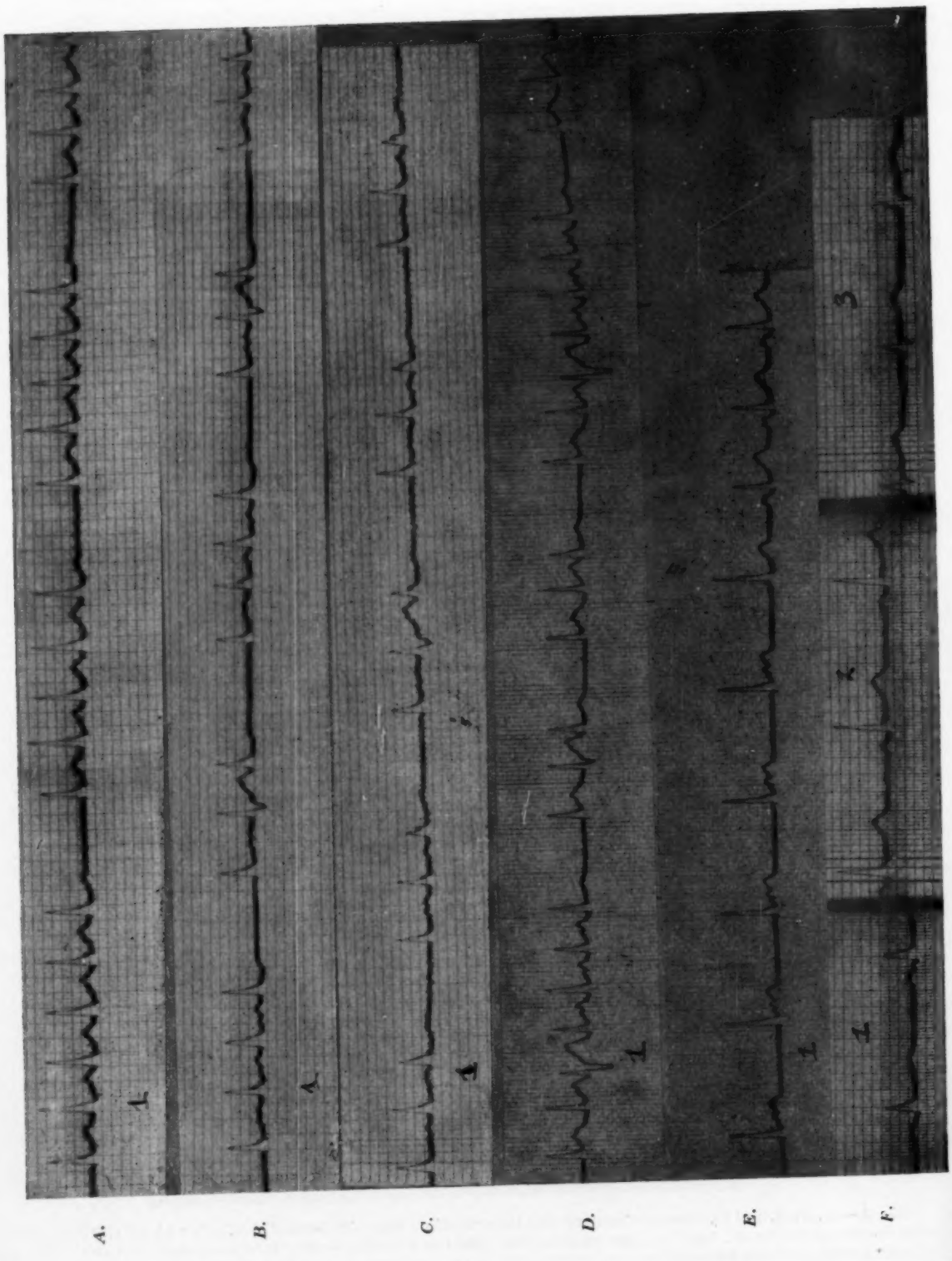


Fig. 3.—(*For legend see opposite page.*)

In addition to this electrocardiographic post-tachycardia syndrome, dilatation of the heart during the attack was demonstrated by radiologic examinations. Furthermore, the strain that these attacks have inflicted on the heart during the years was evidenced by the development of right bundle branch block which was best recorded in V_2 in Figs. 1, *A* and *C*.

At the time of an attack a fast A-V nodal rhythm probably existed, and it is sometimes followed by a slow nodal rhythm (Fig. 3,*E*), but sometimes even at rapid rates P waves were observed following the QRS complexes (Fig. 2, Leads III and aV_L). The fourth injection of procaine amide produced Luciani periods with no P waves evident before the first QRS complex of a group of contractions, the spacing of the first two of which was longer, while the spacing was shortest between the complexes in the middle of the group, and longer at the end of the period (Fig. 3.).

The attacks could never be stopped by ocular or carotid sinus pressure. A few times success was obtained in terminating a paroxysm by ouabain or Digoxin and occasionally by acetylcholine. The best results in interrupting the paroxysms were obtained by quinidine sulfate orally or procaine amide intravenously. The dosage of procaine amide necessary to terminate an attack increased in the course of time. At first 400 mg. was sufficient, later 600 mg. was needed, then 850 mg., and lastly 1,700 mg. was required. After a paroxysm was terminated by quinidine or procaine amide, a normal conduction interval was always observed in electrocardiograms for 16 hours or more. Then without further medication the conduction again changed to that of the W-W-P-W Syndrome. The W-W-P-W characteristics were observed immediately after a spontaneous termination of the paroxysm or when an attack was stopped by acetylcholine or Digoxin. It was possible to convert the W-W-P-W syndrome into normal conduction by quinidine given orally or procaine amide intravenously (Fig. 4, *A* and *B*). This transition was also registered by vectorcardiogram as we published elsewhere.[5] Atropine and Adrenalin had the same effect, but in addition an alternation of both types of complexes was recorded (Fig. 4, *C* and *D*) as described by others (Holzmann[6] and Bellet[1]).

The changes in the electrocardiogram during the treatment with procaine amide during attacks of paroxysmal tachycardia were observed to have altered in the last years. A decrease of the initial rate of 260 to 200 per minute was observed originally after the lower dosage, and at that rate of 200, changes of the QRS complexes were noted (Fig. 2, *E* and *F*). After these changes had occurred the rhythm became normal. Unfortunately the transition between the attack and the normal rhythm was never recorded in the electrocardiograms. Later with the higher dosage, the occurrence of grouped contractions caused by periods of standstill of the heart ranging from 0.75 to 1.0 second were recorded. At first the pauses separated groups of eight contractions, but gradually the number of contractions in a group diminished in number; from eight contractions to seven contractions, etc., until groups of 3 contractions were observed. At one time groups of three were recorded for a period of 19 minutes.

Each time that groups of three were recorded for a while, a change in the QRS complex was noted. This could be possibly explained by an aberrant conduction but also as coupled premature contractions. After the groups of three were present, there followed a nodal rhythm and then a normal rhythm or the rhythm passed directly from groups of three to a normal rhythm, or groups of more contractions reappeared gradually reverting to the original state of paroxysmal tachycardia (Fig. 3). In the latter situation in which the groups returned to the tachycardia instead of to a normal rhythm, a second dose of procaine amide was given intravenously after a few hours, by which the attack was always terminated.

Fig. 3.—Luciani periods. *A*, Groups of six, five, and four beats. No P wave, before the group, no P wave after the last beat. Note that the interval between the first and the second beat of a group is always the longest. *B*, Groups of four and three beats. Perhaps P waves are seen after the first QRS complex of the group. *C*, Note changes of QRS in the group. *D*, After 19 minutes of groups of three beats, groups of more beats reappear. *E*, A-V nodal rhythm seen in the first five beats, normal rhythm in the last three beats. The sixth beat shows a P wave from the sinus node but a QRS complex as shown by the nodal rhythm. *F*, Normal conduction after an attack of nine hours' duration, treated with 1,700 mg. procaine amide, intravenously. Note the absence of the post-tachycardia syndrome. The duration of the attack was too short to give rise to a lack of oxygen sufficient to create the electrocardiographic changes of the post-tachycardia syndrome. As the dose of procaine amide was higher than ever before, it may be concluded that the S-T changes seen at other times are not caused by the procaine amide.

Fig. 3.—(For legend see opposite page.)

These formations of grouped beats were recorded five times. No group was preceded by a P wave, and after the last beat of the group a P wave could not be found with any degree of certainty. The interval between the first and the second beat was widest, the frequency of beats increased toward the middle of the group, and decreased toward the end. During the last attack, observed on Feb. 23, 1954, at 7:30 A.M., 600 mg. procaine amide was given intravenously at 10 A.M. without any effect. At 11 A.M., 400 mg. more was injected, again without effect. When at 5:00 P.M., 700 mg. was again injected slowly, the group forming occurred at once, starting with groups of six and ending with groups of three beats. At 5:10 P.M. after the patient yawned, a slow nodal A-V rhythm appeared, changing again to a normal sinus rhythm (Fig. 3, *E*). The next day, after the procaine amide had lost its effect, the W-W-P-W syndrome reappeared.

Fig. 4.—*A* and *B* after 200 mg. procaine amide, intravenously. *C*, 0.05 mg. atropine sulfate. Conversion of normal conduction to Wolff-Parkinson-White syndrome. *D*, Adrenalin hydrochloride. Alternating of normal beats with beats showing Wolff-Parkinson-White syndrome.

DISCUSSION

The nodal character of the tachycardia observed points to a functional elimination of the influence of the sinus node. Here the condition to which Van Ginkel[4] attached so much importance for the occurrence of the periods of Luciani is complied with. The experiments have also suggested the importance of anoxemia. One can probably accept the fact that after a prolonged attack the oxygen supply of the heart muscle has suffered, as indicated by the post-tachycardia syndrome revealed by the electrocardiogram.

Van Ginkel[4] stressed the fact that deficient oxygen is not imperative and observed, as did De Boer,[2] that various drugs may produce periods of Luciani without deficiency of oxygen.

We believe that procaine amide should be added to the list of these drugs. We only noticed this phenomenon after higher dosage and were impressed by the fact that the longer the attacks lasted, the sooner Luciani periods developed. This could be explained by anoxemia increasing with the duration of the attack. One must keep in mind, however, the cumulative effect of procaine amide.[1]

Experimentally, the phenomenon only occurs when the heart is in poor condition and the disorder, Luciani periods, are observed clinically only after higher dosage of procaine amide with possibly a toxic effect. We are inclined to accept the formation of grouped beats as a caution that further administration of procaine amide should be avoided.

To explain the rhythmicity of the heart the existence is conceived of physico-chemical processes, leading to an accumulation of a chemical substrate or a physical condition, which after reaching a certain level brings about its own destruction or a discharge. Holzmann,[6] Katz,[8] and Van Ginkel[4] are of the opinion that during the periods of Luciani the threshold of excitability at which the discharge occurs changes, as well as the rate of the stimulus formation. The anabolic process of stimulus formation is disturbed, but least so after a pause in which a degree of restoration seems to take place similar to the effect seen in the so-called periods of Wenckebach[10] in which it is accepted that the tissue of the bundle of His after a dropped beat shows an improved conduction. One could imagine that the effect of procaine amide has a depressing effect on the chemical process of stimulus formation, and the effect will be enhanced by lack of oxygen. This explanation presupposes poor condition of the heart muscle and, therefore, calls for the utmost care in the administration of procaine amide.

SUMMARY

In a patient with the Wilson-Wolff-Parkinson-White syndrome, the treatment of attacks of (nodal) paroxysmal tachycardia with procaine amide, has led to the formation of grouped beats, similar to those seen by Luciani in his experiments on the isolated asphyxic frog heart using a Stannius' ligature.

SUMMARIO IN INTERLINGUA

In un patiente con le syndrome de Wilson-Wolff-Parkinson-White, le administration intravenose de amido de procaina como remedio in attaccos de tachycardia paroxysmic (nodal) resultava in le production de pulsos gruppate simile al pulsos gruppate observate per Luciani in su experimentos con le isolate corde asphyxic del rana quando ille applicava le ligatura de Stannius. Nos opina que le formation de pulsos gruppate in consequentia del administration de amido de procaina es un signo que le uso de iste droga deberea esser evitate.

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ETIOLOGY OF HOARSENESS ASSOCIATED WITH MITRAL STENOSIS: IMPROVEMENT FOLLOWING MITRAL SURGERY

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INTRODUCTION

AN unusual but important complication in patients with mitral stenosis has been paralysis of the left recurrent laryngeal nerve. The exact mechanism of its production has been a point of discussion and interest.[1-9] Two major schools of thought have considered why patients with mitral stenosis may develop recurrent laryngeal nerve paralysis. One theory has been that the enlarged left auricle compresses the nerve upward against the aortic arch resulting in injury or degeneration of the nerve fibers. (Orthnor's Theory.[2]) The symptom of hoarseness then follows. Other observers have felt that anatomically this was not possible and more likely the nerve was pinched between an enlarged dilated pulmonary artery and the aorta[1-4,7,9] (Fig. 1). Data, usually taken from the post-mortem examination, have tended to support the theory that enlargement of the pulmonary artery has been the main factor in compression of the nerve rather than that of the enlarged left auricle.[3] Other reported possible mechanisms of production of left recurrent laryngeal nerve paralysis would be its compression between the enlarged auricle and left bronchus[3,4,7] or the nerve could be impinged within the triangle formed by the aortic arch, dilated pulmonary artery, and a strategically located enlarged lymph node.[2,4] Cases of mediastinitis have resulted in the nerve being involved by scar formation, thereby causing paralysis.[3,7,9] Adhesive pericarditis at the base of the heart around the aorta and pulmonary artery likewise could be an etiologic factor.[2,3,7] Other postulated contributing factors have been a thrombus in the left atrium or pulmonary artery and arteriosclerosis of the pulmonary artery and aorta.[3,4,7,9] An enlarged mediastinal, peribronchial, and bronchial gland also have been incriminated.[2,3,7] Still another suggested mechanism has been rotation of the heart coincident with right ventricular hypertrophy in a manner to produce traction of the ligamentum arteriosum and the nerve.[2-4,7]

Recurrent laryngeal nerve paralysis may also occur in types of heart disease other than mitral stenosis. This has occurred with patent ductus arteriosus where the nerve paralysis has been associated with enlargement of the pulmonary

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Received for publication Aug. 23, 1954.

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artery,[3,7] or theoretically, it is possible for the nerve to be squeezed between the origin of an enlarged patent ductus itself and the aorta. Other congenital lesions that have been reported associated with this type of paralysis have been interatrial septal defects[8] and Eisenmenger syndrome. Again, the likelihood of nerve compression between an enlarged pulmonary artery and the aorta would seem likely in such cases.[8-10] Pulmonary artery enlargement has also been reported in cases of arteriosclerotic heart disease having recurrent laryngeal

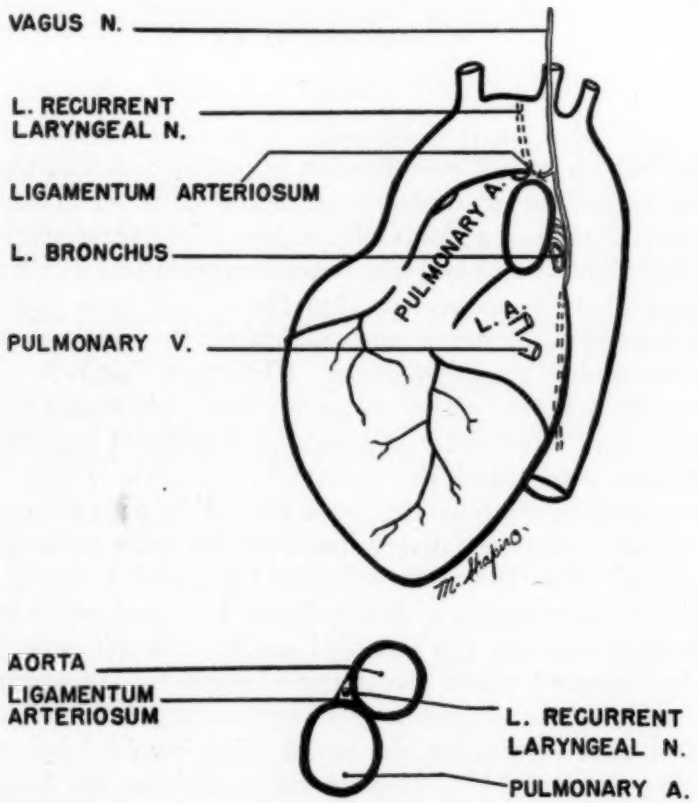

Fig. 1.—Sketch showing mechanism of left recurrent laryngeal nerve paralysis associated with mitral stenosis observed in each of two patients during surgery. Note anatomic relationships where nerve is compressed between enlarged pulmonary artery and the aorta.

nerve paralysis. It was felt that dynamic dilatation of the pulmonary artery during life was playing the most important role since post-mortem examination revealed no significant pulmonary artery enlargement.[5]

The one outstanding association in cases, reported from the literature, based predominantly on autopsy material has been an enlarged pulmonary artery. We have found no reports of observations of the anatomic relationship in living patients at the time of surgery.

Recently we had the opportunity to observe the mechanism of production of recurrent laryngeal nerve paralysis during operation. The etiology was related to pulmonary artery enlargement. The following two cases with rheumatic heart disease and mitral stenosis had hoarseness due to left recurrent laryngeal nerve paralysis. Both underwent mitral commissurotomy.

CASE REPORTS

CASE 1.—A 43-year-old single school teacher was admitted for mitral surgery. She had been in good health until four years prior to admission when she first noted slight exertional dyspnea on climbing stairs. At that time she was told she had a murmur and was digitalized. Two years later because of some progression of symptoms including palpitation, she was seen by another physician who diagnosed mitral stenosis. There was no history of rheumatic fever. She had been able to enter into normal activities as a child and had not restricted herself in any way until the past four years. Ten months before admission she first noted hoarseness, associated with an upper respiratory infection and cough. Her hoarseness continued and became progressively worse until she was unable to carry on her duties as a school teacher. She could talk in a voice only slightly louder than a whisper which was a detriment to teaching.

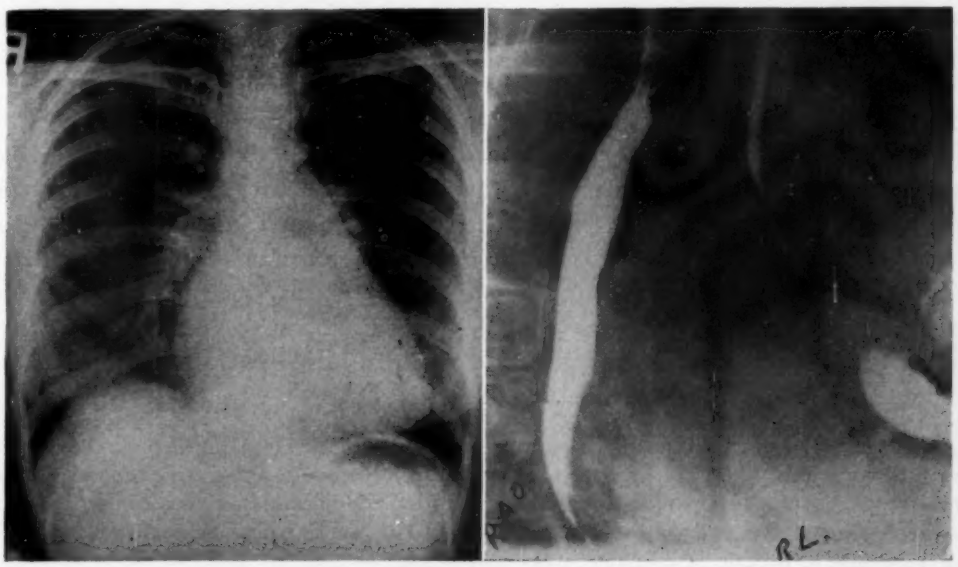

Fig. 2.—43-year-old woman with left recurrent laryngeal nerve paralysis associated with mitral stenosis. Note straightening of left cardiac border with enlarged pulmonary artery segment. Moderate left auricular enlargement demonstrated on barium swallow.

Pertinent findings on physical examination: A white woman in no acute distress, speaking with a hoarse, whispering voice. Blood pressure 100/60 mm. Hg in both arms. Neck veins were not distended. Thyroid was not remarkable. Eye grounds revealed no abnormality. The chest was of normal configuration. The lungs were clear to percussion and auscultation. No râles were heard. The heart was enlarged to percussion, and at the apical area there was a palpable presystolic thrill. The apical rate was 80. The first heart sound was accentuated, and a Grade 4 presystolic crescendo murmur of rumbling quality was heard. An opening snap of mitral stenosis was present. The pulmonic second sound was accentuated. Liver and spleen were not felt. Extremities showed no edema or phlebitis. Indirect vision of vocal cords revealed left cord paralysis with no movement of the arytenoideus. Routine blood work and chemistries were normal. Urinalysis and serology were negative. Electrocardiogram showed normal sinus rhythm. The P waves were large and notched, suggesting auricular enlargement consistent with mitral stenosis. Circulation time arm-to-tongue (Decholin) was 22 seconds. Arm-to-lung time (ether) 16 seconds. Venous pressure was 85 mm. of saline which rose to 87 mm. with right-upper-quadrant pressure. Vital capacity 81 per cent. X-ray and fluoroscopic examination showed mild pulmonary congestion and moderate cardiac enlargement. There was straightening of the left border of the

heart and the pulmonary artery segment was enlarged. On barium swallow the esophagus was noted to be displaced by a moderately enlarged left auricle (Fig. 2).

At the time of surgery the size of the pulmonary artery was found to be twice that of normal. It was noted to be under greater pressure than usually found and on palpation was described as being "very tense and hard." It was clearly evident that the left recurrent laryngeal nerve was compressed between the aortic arch and the distended pulmonary artery (Fig. 1). The mitral valve was exposed, and a tight stenosis was present. It was estimated that the mitral orifice was 5 to 6 mm. in diameter. On fracturing the valve it was observed grossly that the tenseness and pressure of the pulmonary artery quickly and definitely diminished. The recurrent laryngeal nerve appeared to be released from its former state of impingement.

Her post-operative course was essentially uneventful, and she progressively noted improvement in her work tolerance. At the end of eight months, her voice had returned to almost normal and she could perform her duties as a school teacher on a full time basis. Laryngoscopic examination now showed return of some of the motility of the left cord although not completely to normal.

Comment: This case demonstrated that the mechanism of recurrent laryngeal nerve paralysis was due to compression between the enlarged dilated pulmonary artery and the aorta. The relationships of the anatomic structures involved were actually observed at the time of operation, whereas previous reports in the literature have been based either on post-mortem examinations or theory. There was no question in any observer's mind as to the etiology of this patient's hoarseness. Upon fracturing the mitral valve and thereby relieving pressure in the pulmonary artery, the relationships of the nerve, pulmonary artery, and aorta showed a definite change and the nerve was no longer pinched following this procedure.

CASE 2.—A 44-year-old married Negro woman had a chief complaint of progressive hoarseness of three months' duration. She had otherwise been in good health until one month prior to admission when she developed an upper respiratory infection associated with cough, productive of whitish sputum measuring up to one cup a day. Two weeks before, she noticed for the first time shortness of breath on climbing stairs and doing her ordinary housework. She was seen by an otolaryngologist who told her that her hoarseness was due to left vocal cord paralysis. Prior to her present illness she had noted no significant symptoms of congestive failure. There was no history of rheumatic fever, heart murmur, hypertension, cyanosis, or other symptoms of heart disease. She had been treated for syphilis approximately ten years before. Ten pregnancies resulted in seven normal deliveries and three miscarriages, none associated with any cardiac symptomatology.

Pertinent findings on physical examination: A moderately obese female, lying flat in bed, in no distress. She spoke with a faint whisper. Blood pressure 120/80 mm. Hg. Neck vessels were not distended and no abnormal pulsations or thrills were present. Examination of the larynx showed left vocal cord paralysis. The chest was of normal configuration. The lungs were clear to percussion and auscultation. The heart was moderately enlarged to percussion. Apical rate was 75. The rhythm was regular. First heart sound was accentuated, and at the apex a Grade 4 diastolic rumble with a presystolic accentuation was present over a localized area. Over the pulmonic area a Grade 3 systolic murmur was heard. The pulmonic second sound was greatly accentuated and produced a palpable impulse in the second left intercostal space (Fig. 3). The abdomen was obese. No organs were felt. The peripheral pulses were of normal quality. Extremities showed no edema or phlebitis. No cyanosis or clubbing.

Laboratory data: Blood chemistries and urinalysis were within normal limits. Serology was negative. Circulation time (Decholin) arm-to-tongue, 17 seconds; arm-to-lung (ether) 8 seconds. Venous pressure 118 mm. of saline which did not change on right-upper-quadrant pressure. Electrocardiogram showed normal sinus rhythm, complete right bundle branch block, and right

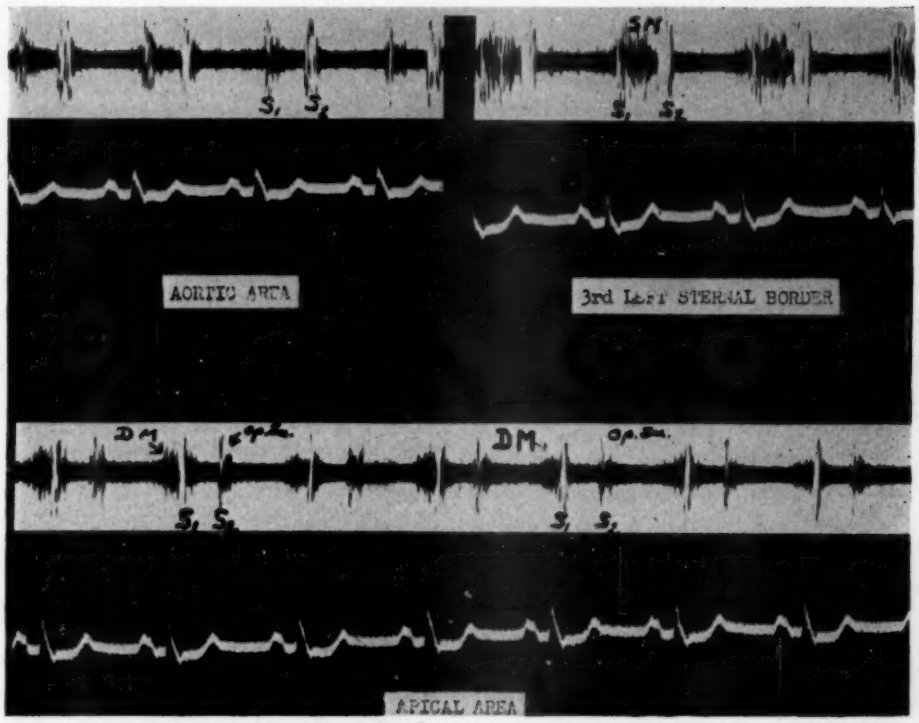

Fig. 3.—44-year-old woman with mitral stenosis. Chief complaint, hoarseness (due to left recurrent laryngeal nerve paralysis). Apical area: First sound (S_1) accentuated, opening snap (op. sn.) followed by diastolic rumble (*DM*) with presystolic accentuation. Third left sternal border: Pulmonic second sound (S_2) accentuated. Note harsh systolic murmur (*SM*).

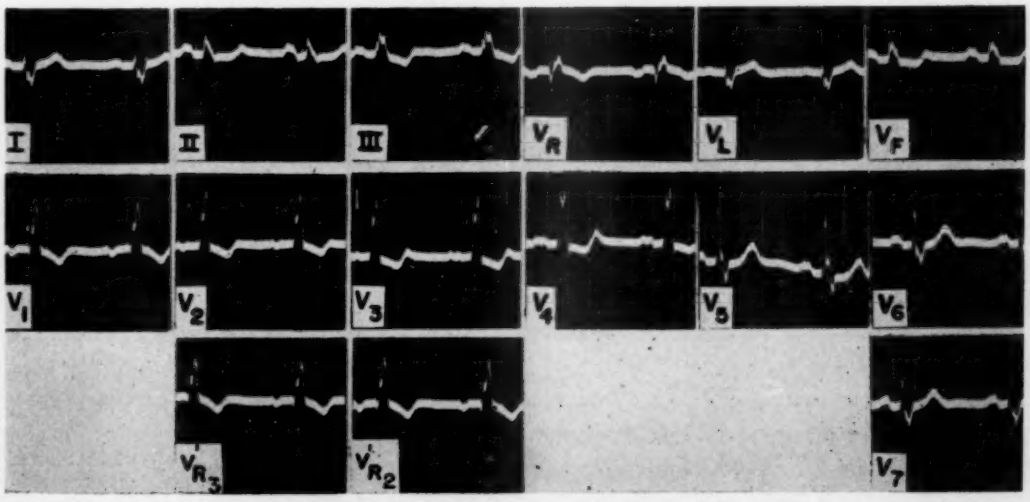

Fig. 4.—Electrocardiogram of same patient as Fig. 3. Note right ventricular hypertrophy, right bundle branch block, and broad notched P waves.

ventricular hypertrophy. Notched P waves of the type commonly seen with mitral stenosis were present (Fig. 4). X-ray and fluoroscopy showed a mild degree of pulmonary congestion, and there was a markedly dilated pulmonary artery segment. Moderate cardiomegaly was present, and barium swallow revealed slight to moderate posterior displacement of the esophagus (Fig. 5).

Because of development of signs of congestive failure and hoarseness related to left recurrent laryngeal paralysis, mitral surgery was performed. At the time of operation she was found to have a very dilated left pulmonary artery compressing the left recurrent laryngeal nerve against the aorta. The nerve itself did not appear grossly abnormal. The mitral valve was "tight" and fracture was accomplished without any difficulty. The postoperative course was essentially uneventful. Follow-up five months later revealed gradual but definite improvement in her voice (although hoarseness persists to a lesser degree).

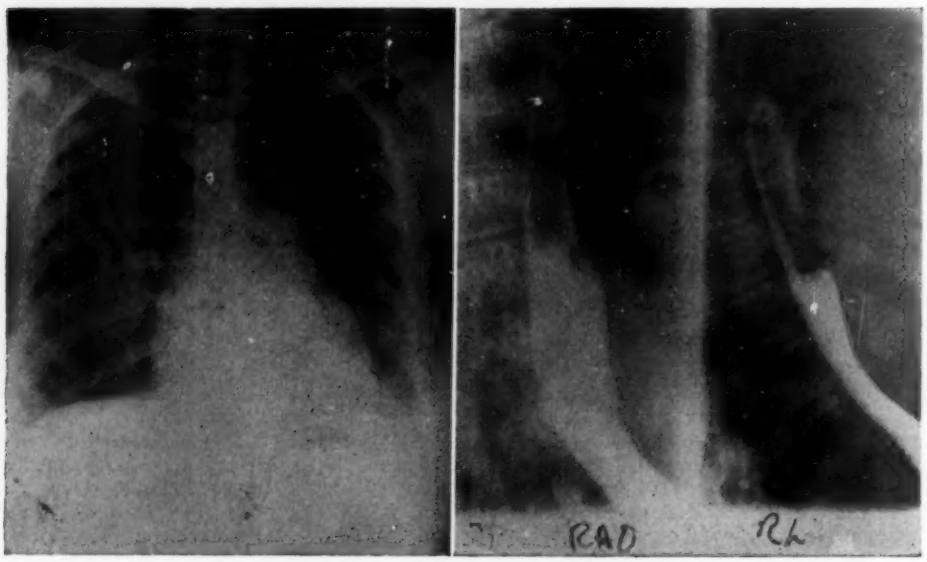

Fig. 5.—Heart films of same patient as Fig. 3. Moderate cardiomegaly with prominent pulmonary artery segment. Barium swallow shows only slight left auricular enlargement.

Comment: Another patient was observed at operation where the mechanism of recurrent laryngeal nerve paralysis appeared to be compression between an enlarged distended pulmonary artery and the aorta. Again as in the previous case the left auricle was apparently playing no role in the production of this paralysis. Her voice function has already started to return. She can now be understood speaking over the telephone whereas formerly this was not the case.

DISCUSSION

The occurrence of left recurrent laryngeal nerve paralysis complicating mitral stenosis is rare. Out of a series of 223 cases of left recurrent laryngeal nerve paralysis only ten had mitral stenosis.[6] On the other hand, a review of 300 cases of mitral stenosis disclosed two cases of nerve paralysis.[2,4] Still another series of 235 patients of left recurrent laryngeal nerve paralysis revealed five associated with heart disease, and thirty-four with aortic aneurysm.[2]

Because the anatomy of the region may vary in every case the anatomic conditions required to produce compression of the nerve may differ accordingly. For example, in some cases an extremely enlarged pulmonary artery may not result in paralysis and on the other hand, hardly demonstrable enlargement may do so. The location of the ligamentum arteriosum, which forms one of the sides of the triangle made by the aortic arch, pulmonary artery, and ligamentum arteriosum, has been suggested as playing a role by fixing the nerve, thereby preventing it from slipping away when pressure is being exerted.[4,5]

The occurrence of left recurrent laryngeal nerve paralysis associated with mitral stenosis is an added indication for mitral surgery. The importance of operating early before permanent damage has taken place in the nerve cannot be overemphasized. However, even after a prolonged period of nerve paralysis it is possible for the voice to return. This was illustrated by the school teacher who following operation regained her speaking voice despite a preoperative ten months' history of hoarseness.

Although other contributing factors and other mechanisms are possible, we feel the enlarged pulmonary artery is a most important cause of recurrent laryngeal nerve paralysis in patients with mitral stenosis.

SUMMARY

Two cases of mitral stenosis associated with hoarseness were improved by mitral surgery. The mechanism of recurrent laryngeal nerve paralysis was proved to be due to an enlarged pulmonary artery. It is felt hoarseness from this etiology is an added indication for mitral commissurotomy.

SUMMARIO IN INTERLINGUA

Es reportate duo casos de stenosis mitral associate con raucitate del voce. In ambe casos le causa del recurrente paralyse del nervo laryngeal esseva demonstratemente le compression del nervo per un allargate arteria pulmonar: in ambe casos le raucitate se meliorava post commissurotomia mitral, evidentemente in consequentia del resultante reduction del pression del arteria pulmonar super le nervo laryngeal. Ben que altere factores contribuente e altere mechanismos causal es possibile, nos crede que un allargate arteria pulmonar representa un importantissime causa de recurrente paralyse del nervo laryngeal in patientes con stenosis mitral. Raucitate del voce con iste etiologia debe esser considerate como un indication additional pro commissurotomia mitral.

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Announcements

A course in ELECTROCARDIOGRAPHIC INTERPRETATION for *graduate physicians* will be given at the Michael Reese Hospital by Louis N. Katz, M.D. (Director of the Cardiovascular Department, Medical Research Institute) and associates. The class will meet daily from 9:00 A.M. to 5:00 P.M., August 22 through September 3, 1955.

Further information and a copy of the lecture schedule may be obtained upon application to Mrs. Ana Rose, Administrative Secretary, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago 16, Illinois.

A post-graduate course on CONGENITAL HEART DISEASES will open in Rio de Janeiro on Sept. 19, 1955. It will be sponsored by the Brazilian Society of Pediatrics and the Faculty of Medicine of the University of Brazil. The course will be conducted by Dr. A. de Carvalho Azevedo and associates and will be divided in two parts: Part 1 concerns the data that may be obtained from the various semiotic procedures: history taking and clinical examination, x-ray examination, electrocardiography, angiocardiography and cardiac catheterization. Part 2 deals with the clinical and surgical aspects of interauricular and interventricular septal defects, patent ductus arteriosus, aortic septal defects, pulmonic stenosis, and the tetralogy of Fallot. For complete information apply to Dr. A. de Carvalho Azevedo, Av. Nilo Peçanha, 38-5° and., Rio de Janeiro, Brazil.

Book Reviews

PERIPHERAL VASCULAR DISEASES. By E. V. Allen, N. W. Barker, and E. A. Hines, Jr., Philadelphia and London, 1955, W. B. Saunders Company.

Because of the recent advances in knowledge and techniques of many of the conditions described, the second edition of this excellent textbook has been overdue for several years. Extensive changes in the organization of material have been made, and this edition has been broadened by the inclusion of more collaborators and especially by an increased number and greater detail of associated surgical procedures. The advances in arteriography and the surgery of aneurysms and segmental arterial occlusion are well presented as timely new material. New chapters on coarctation of the aorta and on purpura are welcome additions to this book.

This edition is slightly shorter than the first but is much better balanced. The inclusion of the new material has been made possible by the omission of the chapters in the first edition on the anatomy of peripheral vessels and those on nailfold capillaries and sweating. New illustrations have been added, but unfortunately there is no increase in the number of those in color. An addition also would be a discussion of the differential diagnosis of chronic leg ulcers. The extensive changes in this edition are all improvements and make this book more than ever the best in the field of peripheral vascular diseases.

J. C. L.

PROBLEME UND BEISPIELE BIOLOGISCHER REGELUNG. By R. Wagner, Stuttgart, 1954, Georg Thieme Verlag.

While in the past decades physiologic research was mainly devoted to the analysis of functional parts of the organism ("Teilapparate"), synthesis of the function of the various parts appears now to be timely, as a bridge for the understanding of the organism as a whole ("Ganzheitsbetrachtung"). In an attempt at such a synthesis, the author uses technical feedback systems as a pattern for the mechanism of physiologic regulations, referring specifically to regulation of voluntary movements (pp. 33 to 123) and circulation (pp. 124 to 207). The problem is well thought through, and there is a wealth of detail but Wagner's book does not reach the perspective and breadth of presentation of Barcoft's monograph on the *Architecture of Physiological Function* (1934). Unfortunately, the language is somewhat involved, which is a distinct handicap in the discussion of complex physiologic situations.

E. S.

REACTIONS WITH DRUG THERAPY. By Dr. Harry L. Alexander. Philadelphia and London, 1955, W. B. Saunders Company, 301 pages, 33 figures.

With drug reactions on the increase, and the advent of more and more new synthetic compounds for therapeutic use, this small volume by Dr. Harry Alexander should be very welcome. The book has eighteen chapters and includes listings of all currently used drugs in addition to those less frequently resorted to. Reactions to pollen extracts, seeds, and oils are also discussed. The main purpose of the book is to reduce what appears to be a rather complex diagnostic problem to one of simpler terms, and this is largely achieved.

The similarity of the various reactions regardless of the type of medication used is emphasized, and the underlying mechanisms are well discussed. Included in this book are the basic chemical formulas of well-known sensitizing agents, showing the relationship of various chemical radicals to potential sensitizing capacity. The more recent knowledge of the probable immune mechanisms is considered in relation to haptens, and the capacity of compounds of small molecular weight to act as antigens.

Although the title of the book refers to all types of reactions to drugs, an attempt is made to differentiate between those on an allergic basis and other forms. The volume is well written and has an excellent bibliography. It is recommended for anyone dealing with the administration of therapeutic agents. General principles of treatment are included.

B. R.

LEG ULCERS, THEIR CAUSES AND TREATMENT. By S. T. Anning, Boston, 1954, Little, Brown & Company.

At first the title of this book is misleading, because it was not until this reviewer began to read it that he realized the extent to which this subject concerns the cardiovascular specialist. The leg ulcers are the last event in a chain of developments most of which fall definitely within the scope of "Cardiology." The author fully discusses these factors: arterial disease, venous disease, including varicosities, causes of disturbed circulation in the leg, venous thrombosis arising either from changes in the wall of the veins or in the clotting tendencies of the blood. The book is really a comprehensive discussion of circulatory disturbances of the leg in relation to the venous circulation. As such it can warmly be recommended as part of the physician's library. The book is beautifully written and well arranged, and the publishers are to be congratulated.

J. J.

L'APPARATO CARDIOVASCOLARE NELLA BRUCELLOSI (THE CARDIOVASCULAR SYSTEM IN BRUCELLOSIS). By M. Poli, Pisa, 1953, Edizione Omnia Medica, 179 pages and 6 figures.

This monograph analyzes the various cardiovascular lesions caused by *Brucella melitensis* and the resulting clinical pictures, and tries to establish their relative frequency. Endocardial, myocardial, and pericardial lesions during brucellosis have been repeatedly reported. Out of 166 cases of brucellosis observed by the author, 80 presented evidence of cardiovascular lesions. However, only in 10 could other etiologic causes be definitely excluded. The other patients may have had cardiac lesions due to brucellosis, but previous rheumatic lesions in patients with brucellosis could not be excluded.

Endocarditis is usually severe and malignant. It can be diagnosed if the valvular lesions are in evolution and blood cultures reveal only brucellae. However, in one case a mixed etiology (*Str. viridans* and *brucella*) was demonstrated. In general, the aortic valve is the most common localization.

Atrial fibrillation, bundle branch or I.V. block, or S-T and T changes reveal, according to the author, the onset of brucellar myocarditis. Fifteen autopsied cases revealed endocarditis in 33 per cent, pericarditis in 33 per cent, and myocarditis in 40 per cent.

Detailed therapeutic considerations follow.

This book is of interest to the internist and the cardiologist. A more clear presentation and a better final summarization, however, would have increased its utility.

A.A.L

Note

In the March, 1955, issue of the AMERICAN HEART JOURNAL (49:367-384) there appeared an article by Doctors A. R. Dawe and P. R. Morrison, entitled "Characteristics of the Hibernating Heart." At the time this article was written, the authors were unaware of previous work that had been done in this field by Doctor H. S. Samuli Sarajas, of Nortulls Hospital, Stockholm, Sweden, reported in the Acta Physiologica Scandinavica, 1:43, 1954. Dr. Dawe has now asked that a note to this effect appear in the AMERICAN HEART JOURNAL.

Editor.